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VAGINAL CYSTS.

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Vaginal cysts have long been recognized and accorded a very thorough consideration. Among the more important contributions on this subject are the articles of Breisky, v. Winckel, Freund, Veit, Stokes, Gebhard, and Bandler. In Vol. VII of the Johns Hopkins Hospital Reports Ernest Stokes gave a careful résumé of the literature and reported eleven cases. Since that time many new specimens have been received so that the total number examined at the hospital including those reported by my colleague Stokes amounted to fifty-three on January 1, 1904. In order to facilitate a satisfactory consideration of the subject it may be well to speak briefly of (1) the gross and histological anatomy of the normal vagina; (2) the embryonic structures that may persist in the vagina; (3) changes in the vagina incident to vaginitis; (4) changes due to injuries resulting from childbirth; (5) alterations in the vagina caused by perineal operations; (6) the relation of the urethra to the vagina.

(1) The Normal Vagina.

The lining of the cavity is composed of several layers of squamous epithelium of which the more superficial near the outlet tend to become horny. The deepest layer which rests on the underlying stroma consists of cells, cuboidal or low cylindrical in type. The stroma is made up of fibrous tissue poor in cell elements, but as a rule with a well-developed blood supply. Small tufts of the stroma project up into the epithelium producing the so-called papillæ. The vaginal mucosa resembles very closely the normal skin. The pigment in the deep layers is, however, usually wanting.

Vaginal Glands.—The existence of vaginal glands has been much questioned, but v. Preuschen in 1877 after a careful examination of thirty-six bodies found definite vaginal glands in four. The necks of these glands are lined by squamous epithelium, while the deeper portions, which spread out into definite bays, are lined by cylindrical epithelium on which cilia may be detected. Opening into the dilated glands are little crypts. Similar glands had previously been noticed in 1870 by Hennig. In Path. No. 955, where we were dealing with a small cyst 6 mm. in diameter and lined by one layer of cuboidal epithelium, I found a small oval gland-space lined with one layer of high cylindrical epithelium (Fig. 1). It closely resembled a cervical gland and was surrounded by a definite inflammatory zone.

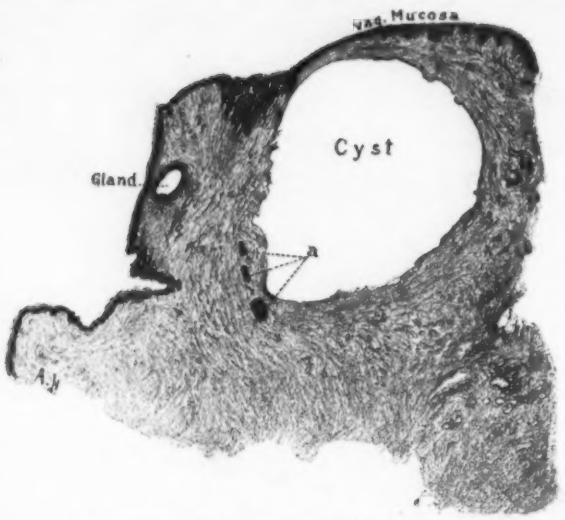

FIG. 1.—A VAGINAL GLAND (10 DIAMETERS).

Gyn.-Path. No. 955. Lying beneath the slightly atrophic mucosa, is a vaginal cyst, 6 mm. in diameter. Immediately beneath the vaginal epithelium is a small gland. This was lined with high cylindrical epithelium resembling that of a cervical gland. The dark areas (*a*) represent small masses of normal vaginal epithelium.

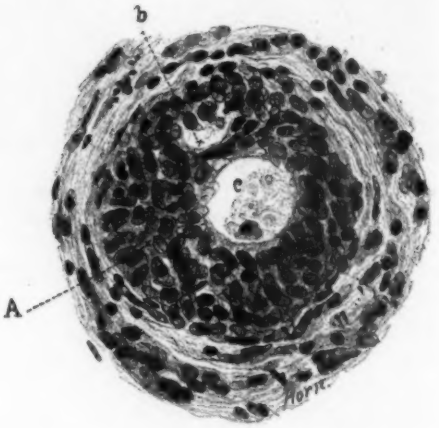

FIG. 2.—UNUSUAL EPITHELIAL ELEMENTS IN THE POSTERIOR VAGINAL WALL (480 DIAMETERS).

In this case there was a complete perineal tear with two minute vaginal cysts lined with squamous epithelium. In the immediate vicinity was the nest of cells which are seen at *A*. These cells have oval nuclei and show a distinct glandular arrangement (*b* and *c*). Surrounding this group of cells is the ordinary connective tissue of the vagina.

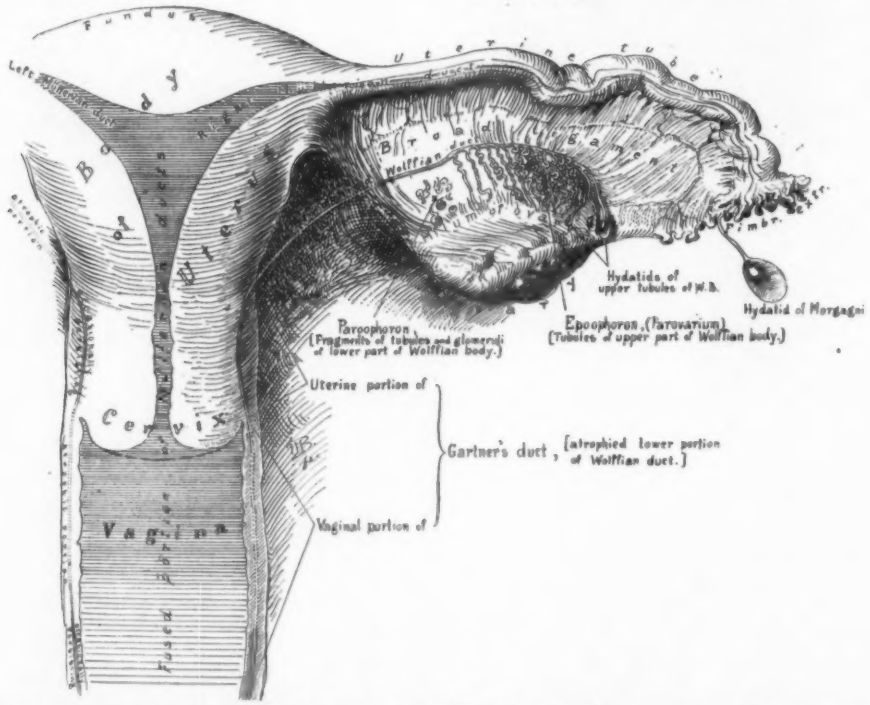

FIG. 3.—A SCHEMATIC ILLUSTRATION OF THE FORMATION OF THE UTERUS, THE TUBES, AND THE VAGINA, AND OF THE RELATION OF THE WOLFFIAN AND GARTNER'S DUCTS TO THE BROAD LIGAMENT, UTERUS AND VAGINA.

The outer portions of Müller's ducts form the Fallopian tubes. The middle portions unite to form the uterus and the distal portions form the vagina. In the broad ligament between the tube and ovary we see the epoophoron or parovarium composed of many cork-screw-shaped tubules and communicating along the upper extremities with the collecting duct. They represent the tubules of the upper part of the Wolffian body. Lying embedded at the inner side of the hilum of the ovary are fragments of tubules and glomeruli of the lower part of the Wolffian body. In the drawing Gartner's duct can be traced obliquely down through the broad ligament into the uterus near the internal os. It can be followed through the outer portion of the cervix to the vagina. As a rule, the vaginal, uterine, and inner broad ligament portions disappear.

We were unable to tell whether the cyst was situated in the anterior or posterior vaginal wall.

In Path. No. 5593 there was a complete tear of the perineum and situated in scar tissue were two minute vaginal cysts lined with squamous epithelium. In the vicinity can be seen an almost circular nest of cells with oval vesicular nuclei (Fig. 2). In this mass of cells are two definite gland-spaces around which the cells appear to be cuboidal or low cylindrical in type. We are at a loss to explain the presence of this group of cells, particularly as they were situated in the posterior vaginal wall where a complete tear existed. They were too far away from the rectum and surrounded by too broad a zone of fibrous tissue to have originated in any way from the bowel. Furthermore their appearance did not suggest any relationship to rectal epithelium.

From the foregoing there seems to be no doubt that vaginal glands exist in a moderate percentage of women.

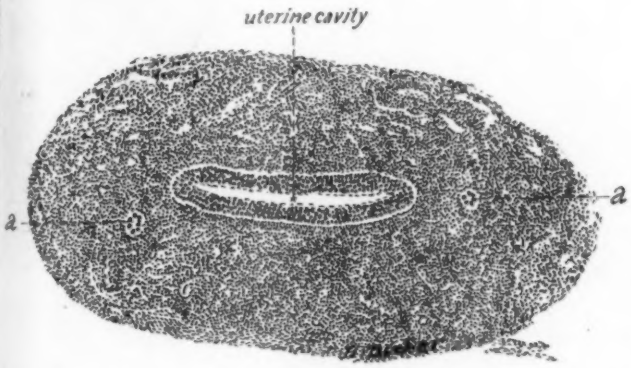

FIG. 4.—A CROSS SECTION OF THE UTERUS NEAR THE CERVIX SHOWING GARTNER'S DUCT ON EACH SIDE OF THE UTERINE CAVITY (FŒTUS AT THE END OF 3D MONTH).

The uterine cavity is represented by a long slit lined by several layers of epithelium. Gartner's ducts are situated well toward the outer side of the uterus, are circular and lined with one layer of cuboidal epithelium. The uterine muscle is not as yet well differentiated.

(2) EMBRYONIC STRUCTURES THAT MAY PERSIST IN THE VAGINA.

(*a*) Gartner's duct.

(*b*) Remains of Müller's duct.

(*c*) Misplaced ureter.

(*a*) *Persistence of Gartner's Duct.*—In the embryo remains of the Wolffian body are recognized as the parovarial tubules situated between the tube and ovary. The duct is continued downward through the broad ligament along the side of or in the substance of the uterus as Gartner's duct. It lies in the substance of the cervix near its outer side and then extends down the anterior or lateral wall of the vagina nearly to the outlet (Fig. 3).

In Fig. 4 we have a cross-section of the uterus in a human embryo at the end of the third month. On either side of the uterine cavity a cross-section of Gartner's duct is clearly shown.

Although it is sometimes possible to trace the duct nearly its entire length in the human being, as a rule, only the upper portion is visible and this in time usually disappears. The structure is best studied in the cow, as in this animal the duct is easily traced. Bland-Sutton gives us a very good illustration (Fig. 5) of Gartner's duct extending down the side of the cervix and in the lateral wall of the vagina forming two distinct cystic dilatations.

Remnants of Gartner's duct are sometimes recognized as one or more disconnected segments following the usual course of the duct along the lateral wall or roof of the vagina to

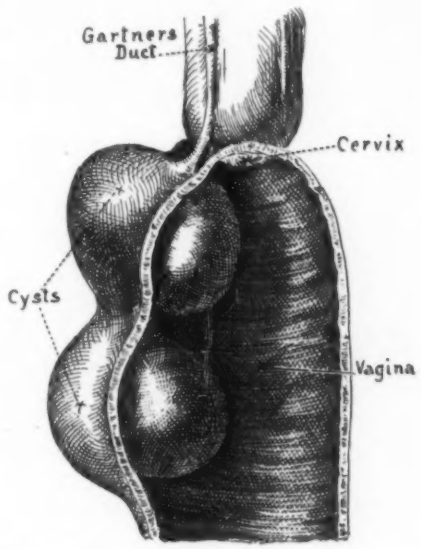

FIG. 5.—VAGINAL CYSTS IN A COW; DUE TO DILATATIONS OF GARTNER'S DUCT.

Passing down the outer side of the cervix are Gartner's ducts. The duct on the left shows two distinct dilatations in the vagina producing typical vaginal cysts (Re-drawn after Bland-Sutton. Published by Keener & Co., Chicago, 1903).

the cervix. In some instances it has been possible to trace the duct from the vagina up to the parovarium. In other words, it was patent for its entire length.

A cross-section of the duct will show an outer covering of fibrous tissue, a middle zone of non-striped muscle arranged longitudinally, transversely or running in both directions, and an inner lining of one layer of cuboidal or cylindrical epithelium.

(*b*) *Remains of Müller's Ducts in the Vagina.*—In some instances Müller's ducts fail to meet. We then may have two uteri and two vaginæ. In other cases the ducts are separate in their upper portions and partially unite at the cervix.

Thus we may have a bicornate uterus with two cervices and two vaginæ or a bicornate uterus with one cervix and one vagina. Other minor variations resulting from failure of Müller's ducts to unite occur, but we are here chiefly interested in the variety where one uterus is fairly well developed, while a second is represented by a rudimentary cord or a

very imperfectly formed organ. The corresponding vagina becomes fused with the lateral wall of the well-developed one. Secretions accumulate in this rudimentary vagina, until it resembles a cystic tumor springing from the lateral wall of the vagina (Fig. 6).

Sometimes its accompanying uterus has been fairly well developed and may communicate with it. In these cases the retained menstrual flow distends the blind vaginal pouch and when the sac is opened, it is found filled with chocolate-colored fluid (Fig. 7). Sometimes the tension becomes so great that eventually a small opening forms and the fluid escapes through the vagina. Such sacs may also become infected before they open. Attention to these rudimentary vaginæ situated in the wall of a well-developed vagina was directed by W. A. Freund in 1877. In his paper he reported several such cases. Kleinwächter shortly after Freund's article reported similar instances.

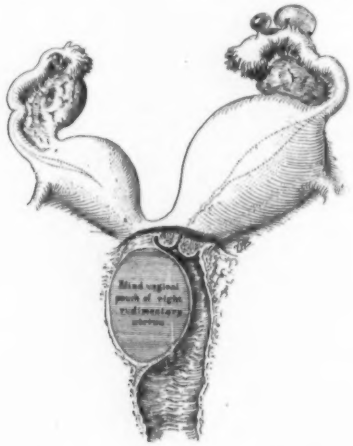

FIG. 6.—RUDIMENTARY VAGINA IN THE WALL OF A WELL FORMED VAGINA.

A schematic illustration of a blind vaginal pouch due to imperfect union of Müller's ducts. The left uterus is well developed and its corresponding vagina perfectly formed. The right uterus is rudimentary and in its cervical portion is represented by a solid cord. The vagina is seen as a blind cystic pouch. Such cavities may collapse, but if distended contain quantities of exfoliated squamous epithelium.

(*c*) *Abnormal Relation of the Ureter to the Vagina.*—When the ureter is in its normal situation its relation to the vagina is not an intimate one, but occasionally a case is met with in which in one lateral wall a small cystic prominence is detected, from which when opened an escape of urine takes place. In other rare instances a fistulous opening into the lateral vaginal wall has been found through which there was a constant discharge of urine. Where any history of injury to the vagina is excluded, which could possibly have caused a fistulous opening between the normal ureter and the vagina, we are probably dealing with an embryonic abnormality. The latter alternative is more probable where there is a double ureter on the one side. Broedel and others have pointed out that where two ureters and two kidneys exist on one side the ureter from the lower kidney is usually inserted at the normal site, while the one connected with the upper kidney is carried down further with the Wolffian duct and is inserted more medialward and nearer the inner urethral orifice. It only would be necessary for this second ureter to be carried down a little further to have it open into or form a blind pouch in the vagina.

(3) CHANGES IN THE VAGINA INCIDENT TO VAGINITIS.

Adhesive vaginitis occasionally occurs, especially in young individuals. Here, as a result of an ulcerative process or a very severe grade of inflammation associated with loss of the vaginal epithelium, the vaginal folds become adherent to one another, producing blind pockets. Such a vaginitis may be due to a general systemic infection, to gangrene following the presence of a foreign body in the vagina or to the highly irri-

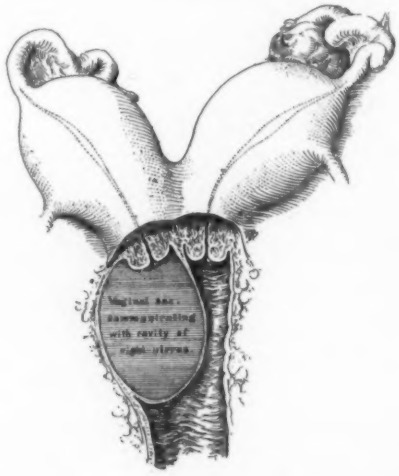

FIG. 7.—A VAGINAL POUCH COMMUNICATING WITH ITS UTERUS BUT NOT WITH THE WELL FORMED VAGINA.

A schematic representation of a condition that sometimes occurs where the vaginal portion of Müller's ducts have failed to fuse. The uteri have developed separately. The vagina proper has been formed from the lower portion of the left Müller's duct. The right vagina, although communicating with its corresponding uterus, has no outlet. The sac is invariably filled with chocolate-colored contents, the remains of menstrual blood.

tative urine where inflammation of the bladder exists. These vaginal occlusions may have a definite bearing on the future development of vaginal cysts.

(4) CHANGES IN THE VAGINA DUE TO INJURIES AT CHILDBIRTH.

The different degrees of laceration of the perineum during labor are well known. Sometimes without any external laceration there may be one or more tears in the mucosa within the outlet. Again there may be a minor or a very extensive laceration of the entire perineum. In many cases, not only are the tears deep but the injury has occurred in such a manner that little tags of mucosa lie partially detached, and during the subsequent healing of the perineum these may

be turned in and included between the edges of the wound. Under these circumstances we have squamous epithelium buried in the perineum; that is, lying in the tissue from 1 to 5 mm. beneath the surface. A similar fate of the small tags of mucosa may also follow even when the perineum is immediately repaired.

(5) Alterations in the Continuity of the Vaginal Mucosa caused by Perineal Operations.

Where it is deemed advisable to repair the outlet some time after labor, after having mapped out a line of denudation it is necessary to remove a large area of vaginal mucosa. But if this is cut away piecemeal instead of in long strips or where the field of operation is not kept perfectly clear, small fragments of the mucosa may be left behind (Fig. 8).

When the edges of the wound are approximated these islands of mucosa lie more or less deeply embedded in the underlying stroma and entirely cut off from the parent mucosa.

FIG. 8.—A FRAGMENT OF VAGINAL MUCOSA THAT MAY GIVE RISE TO AN INCLUSION CYST.

The sketch gives the usual outlines of denudation in a perineal operation. At *a*, a small island of mucosa has been overlooked. When the parts are brought together this will lie deeply embedded and could readily be the starting point of a vaginal cyst.

(6) The Relation of the Urethra to the Vagina.

It is very important to have a clear understanding of the relation of the vagina to the urethra, as over a considerable distance they are intimately associated. Furthermore, as will be seen later, certain cyst-like dilatations arising from the floor of the urethra should not be confused with vaginal cysts although at first sight they may bear a striking similarity. Disse in v. Bardeleben's Anatomy has given us a very clear description of the urethra which I will quote: "The posterior wall of the urethra is firmly attached to the anterior vaginal wall throughout its entire length. Both canals run parallel to each other. The epithelium of the urethra is about .1 mm. thick. The superficial layers of cells are all composed of squamous epithelium. The cells of the deeper layers are more club-shaped. The mucosa is longitudinally folded and as a result club-shaped and tubular depressions are produced. Some of these are simple lacunæ, others are glandular in nature and secrete a colloid material which may in time form concretions. The lacunæ are found in the entire length of the urethra. The smaller ones are broad-based and open by a narrow channel into the urethra. The larger ones are tubular, push into the propria, often branch and tend to run parallel with the surface. These are the glands that sometimes produce the hardened secretion. They are termed Littré's glands." On either side of the urethra are Skene's ducts, which must also be remembered in a consideration of vaginal cysts.

Vaginal Cysts.

It is rather difficult to classify all vaginal cysts according to their origin and the accompanying figures should be accepted only as representing an approximate ratio of the different varieties to each other. I have examined in all fifty-three cases and in a few of these two cysts were present in the same individual.

FIG. 9.—A SMALL INCLUSION CYST (NATURAL SIZE).

Gyn.-Path. No. 5509. A small piece of tissue from the floor of the vagina. It is traversed by several scars as is well seen at *a*. At *b* a small vaginal cyst projects slightly from the surface. In the deep tissue it spreads out. The cyst was lined with several layers of squamous epithelium.

Variety of Cysts.—In twenty-six the origin was clearly the result of a perineal tear or of a perineal operation.

Four seemed to originate from vaginal glands.

Eleven were apparently derivatives of Gartner's duct.

Three were situated near the external orifice of the urethra.

In eight it was impossible to determine the mode of origin.

Inclusion Cysts.—(Those due to small portions of the vaginal mucosa being included in the stroma.) Such cysts are relatively small and are naturally found in the posterior or in the lower lateral wall of the vagina. They are often situated in the scar tissue of an old tear (Fig. 9) or may form a globular mass projecting from the posterior vaginal wall and covered by normal vaginal mucosa (Fig. 10).

In our cases the cysts varied from 3 mm. to 2.5 cm. in diameter. The smaller ones were yellowish in color, the larger more whitish in appearance.

The cyst walls vary from 2 to 4 mm. in thickness; the inner surface is smooth. The cyst contents vary slightly. The smaller ones are often completely filled with a friable material which gives a yellowish tinge to the cyst. This at first sight

slightly resembles pus, but in reality represents masses of exfoliated squamous epithelium.

On histological examination the vaginal mucosa over the surface of the cyst is usually normal, but as might be surmised over the most prominent part it is often slightly atrophic. The cyst walls are composed of fibrous tissue; the inner surface is lined with a varying number of layers of squamous epithelium. Sometimes there is a uniform covering of from 2 to 30 layers of cells, but as a rule the epithelial lining is very thick at one part of the cyst and thin at a distant point. The superficial epithelial cells are often devoid of nuclei and are filled with vacuoles. The deepest layer is usually cuboidal.

The cysts contain desquamated squamous epithelium, detritus, and at times fat droplets and cholesterin crystals. Where the cysts are relatively large the cavity is often partially filled with clear fluid. These cysts are usually single, but they may be multiple, as in Path. No. 3321 (Fig. 11). Here we have three small irregular cysts separated by very slender partitions. They were lined with from 2 to 8 layers of squamous epithelium.

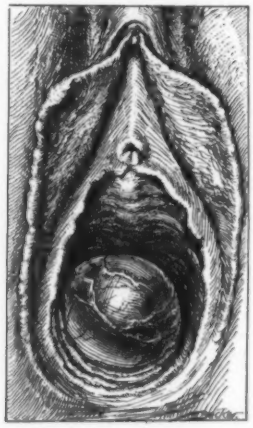

FIG. 10.—A VAGINAL CYST OCCURRING THREE YEARS AFTER REPAIR OF A PERINEAL TEAR.

Gyn.-Path. No. 1504. This cyst contained clear fluid and was lined with several layers of squamous epithelium. It was probably an inclusion cyst.

As has been so clearly pointed out by Stokes and others, little doubt remains that these cysts originate from inclusions of the vaginal epithelium. Our own observations fully substantiate this view. In twenty-four out of the twenty-six of these cases we were able to get a satisfactory history and in every instance the patient had a lacerated perineum and in five out of the twenty-four the perineal tear extended into the rectum. In every case where the site of the cyst was noted it was found either in the posterior or lateral wall, usually in the floor of the perineum.

In Path. No. 298 I noticed a most unusual picture in the cyst wall just beneath the lining epithelium. Here the fibrous tissue was very dense and contained numerous giant cells, some with nuclei in the center of the cell, others with the nuclei arranged peripherally, while the centers of a few contained large, faintly granular masses. The picture in no way suggested tuberculosis.

Cysts probably originating from Vaginal Glands.—Cysts of this origin are apparently less common. Three of our cases seem to fall under this category and possibly a fourth. In Path. No. 2131 A there was a cyst, 6 mm. in diameter, situated in the scar tissue of an old perineal tear. It was lined with cuboidal or almost flat epithelium. Associated with it was a small cyst of exactly the same size and lined with several layers of squamous epithelium. The first cyst, from its situation and epithelial lining, was in all probability a cystic vaginal gland. In Path. No. 2133 B there was also a small cyst in the posterior vaginal sulcus lying near the scar in an old perineal tear and lined with cuboidal cells. The cyst cavity was partly filled with mucus. In this case also there was a small accompanying inclusion cyst. Path. No. 2890 affords another example of a cystic vaginal gland. Here in the scar tissue of the vagina was a cyst 1.5 cm. in diameter lined with very low cuboidal epithelium which secreted mucus.

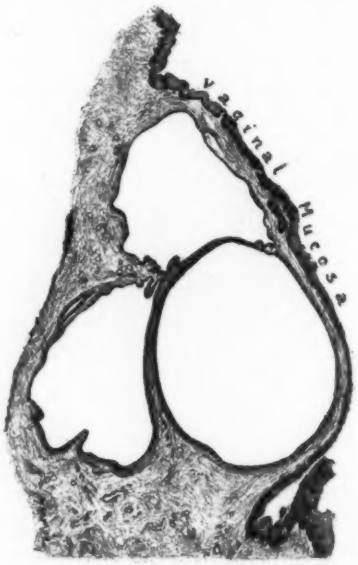

FIG. 11.—MULTIPLE VAGINAL CYST (6 DIAMETERS).

Gyn.-Path. No. 3321. These cysts were associated with a perineal tear, were situated in the left vaginal wall and were lined with from two to eight layers of squamous epithelium. The lower two are irregular in outline and have little tufts of stroma projecting into them.

In Path. No. 2930 there had been a complete tear of the perineum. There were two very small vaginal cysts lying side by side and lined with cuboidal epithelium (Fig. 13). These were probably cystic vaginal glands, but this is only surmise as the exact position of the cyst was not given. In Path. Nos. 2131 A and 2133 B and 2890 I think we have a right to assume that the cysts were derived from the vaginal glands, since with the exception of the latter no other cylindri-

cal or cuboidal epithelial structures are found in this region. Of course it might be said that the cyst was primarily lined with squamous epithelium and that this had exfoliated, leaving only the deepest layer of cuboidal cells; but had this been the case, we would still find evidence of exfoliated squamous epithelium in the cyst cavity. The most convincing evidence, however, is furnished by the fact that we have clear-cut types of two varieties of cysts, the inclusion cyst and that derived from vaginal glands lying side by side without any evidences of degenerative changes in either of them.

Cysts of Gartner's Duct.—As has already been pointed out, in the fœtus Gartner's duct may in some instances pass from the parovarium down the side of or in the substance of the

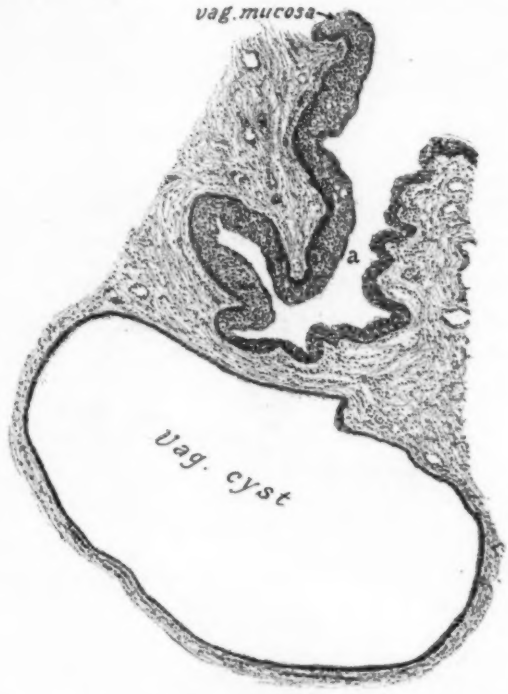

FIG. 12.—A SMALL VAGINAL CYST EMBEDDED IN SCAR TISSUE (40 DIAMETERS).

Gyn.-Path. No. 3690. The cyst was 1.5 cm. in diameter, associated with a perineal tear and embedded in scar tissue. It is lined with from 1 to 7 layers of fairly well defined squamous epithelium. It is situated at the bottom of the vaginal cleft (*a*) and probably at one time communicated with it.

uterus to the cervix and thence obliquely downward and inward to the hymen (Fig. 3). In the vagina its course may run just to the side of the urethra or in the lateral wall of the vagina. We also know that, while in the majority of cases this duct disappears, in a few instances isolated portions persist in adult life. Such isolated links of the persisting duct may as a result of accumulated secretions become cystic. Numerous such examples are on record. If only one segment of the duct persist, a single cyst develops, but should five or six be present, we may have a corresponding number of cysts which, as we should naturally suppose, occur in a single row. The cysts may be exceedingly small, but as a rule reach several centimeters in diameter. In rare instances they almost completely block the vagina. They naturally

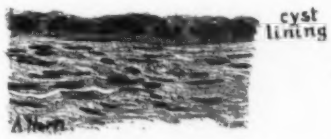

FIG. 13.—EPITHELIAL LINING OF A SMALL CYST IN THE POSTERIOR VAGINAL WALL (480 DIAMETERS).

Gyn.-Path. No. 2930. The cyst lining consists of one layer of cuboidal cells with oval nuclei. These rest on the connective tissue stroma forming the cyst wall.

have an outer covering of vaginal mucosa which over the most prominent part may be atrophic. The cyst walls are usually not more than 1 or 2 mm. in thickness. The inner surface

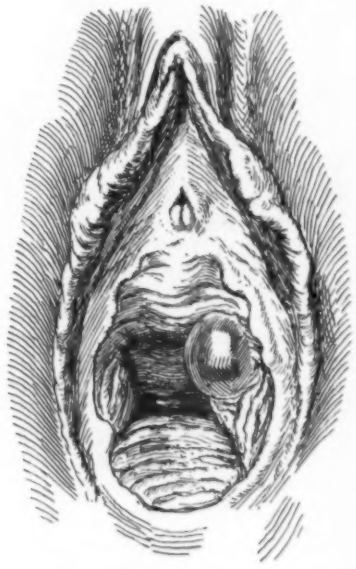

FIG. 14.—VAGINAL CYSTS, PROBABLY ORIGINATING FROM GARTNER'S DUCT (NATURAL SIZE).

Gyn.-Path. No. 3107. The cyst is situated in the left side of the vaginal vault just within the vaginal orifice. It has a smooth surface, its inner surface was lined with one layer of cuboidal cells. Its situation strongly suggests an origin from Gartner's duct.

of the cyst may be perfectly circular, but is frequently oblong and now and then a cyst is met with in which there is a small stem, as it were, leading off from the main cyst (Fig. 16). Such a finding would demonstrate fairly conclusively that a portion of the duct has not yielded so readily to the process of dilatation.

The inner surface of the cyst may be perfectly smooth along its convex vaginal surface, and yet present a definite undulating surface on the opposite or fixed side, showing clearly an unequal dilatation and differing thus from an ordinary cyst. Fig. 17 demonstrates this clearly.

Occasionally we meet with an oblong cyst, as in Path. No. 1775, where the tumor measured 8 x 5 cm. The inner surface presented a definite wavy appearance, being gathered up

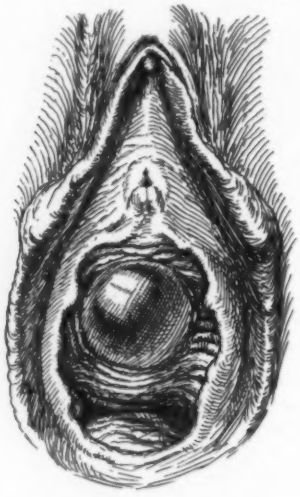

FIG. 15.—CYST IN THE ANTERIOR VAGINAL WALL.

Gyn.-Path. No. 640. Situated beneath the urethra is a translucent cyst. On being dissected out this was found to measure 4.5 × 3.5 cm. Its inner surface was smooth and glistening and it was lined with one layer of flat cells. This cyst was in all probability a dilated portion of a Gartner's duct.

into large and small folds. The cysts are invariably translucent and contain a clear straw-colored or pale fluid.

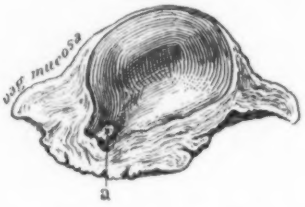

FIG. 16.—SMALL CYST SHOWING IRREGULAR DILATATION.

Gyn.-Path. No. 2878. Covering the surface is vaginal mucosa. The cyst has a smooth inner surface but has distended unevenly. For example, at *a* there is a little pocket that projects downward from the main cyst. Such pictures are relatively common in cysts of Gartner's duct, as one portion of the duct may dilate more than a neighboring segment. The cyst was lined with one layer of cylindrical epithelium. For a low power picture see Fig. 17.

In eleven of our cases a dilatation of a portion of Gartner's duct appears to have been responsible for the cyst. In ten of these the position of the cyst was ascertained. In the remaining one the anatomical peculiarities afforded a sufficient clue for the diagnosis. The most common situation was in the anterior vaginal wall just behind the urethral orifice.

As regards ten of our cases the distribution was as follows:

In the anterior vaginal wall near the urethra, six cases.

In the right lateral vaginal wall, one case.

In the left vaginal wall, one case.

In the right vaginal fornix, one case.

In the left vaginal fornix, one case.

Fig. 15 is a characteristic example of a cyst situated just beneath the urethra. Only rarely do the cysts become pedunculated. Where the cyst is situated in the vaginal fornix

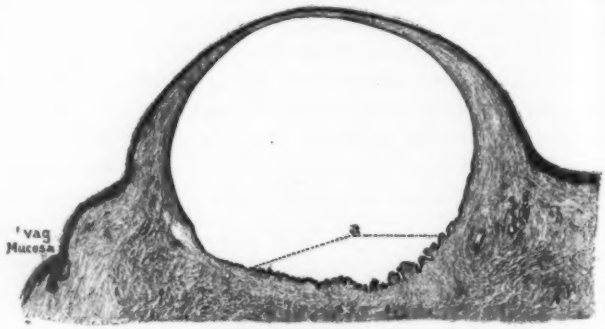

FIG. 17.—VAGINAL CYST, PROBABLY ORIGINATING FROM GARTNER'S DUCT (6 DIAMETERS).

Gyn.-Path. No. 2878. For the natural size see Fig. 16. Covering the surface of the cyst is the vaginal mucosa. This at the sides is normal, over the most prominent part atrophic. The free side of the cyst is smooth, that on the fixed side is gathered up into the folds as shown at *a*. Where inclusion cysts or cysts originating from vaginal glands exist there is equal distension.

the walls are liable to be considerably thicker as the duct lies more deeply embedded in the tissue.

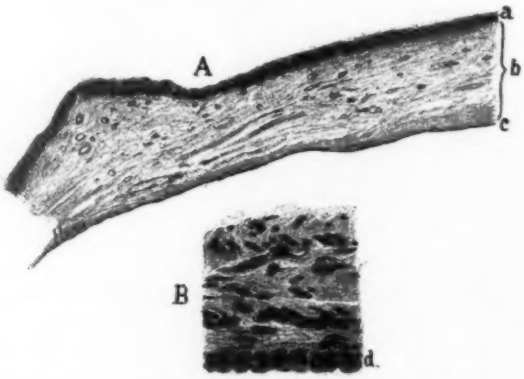

FIG. 18.—A CYST OF THE ANTERIOR VAGINAL WALL.

Gyn.-Path. No. 4644. *A* is a 15 diameter enlargement of the wall. The outer vaginal covering (*a*) is normal. The walls (*b*) are composed of fibrous tissue and the inner surface (*c*) has a delicate lining. *B* is a 408 diameter picture of a portion of *A* and at *d* one sees the inner cyst lining composed of a single layer of cuboidal epithelium.

The cyst walls proper are composed of fibrous tissue; sometimes intermingled with these are bundles of non-striped muscle fiber. These were demonstrated in two of our cases. Where the cyst is small it is often possible to make them out, but in those of large size the muscle is so spread out that sections from various portions of the wall often fail to reveal it although at other points it may be present. The inner surface of the cyst is lined with one layer of cylindrical, cuboidal, or almost flat epithelium.

In the majority of our cases the epithelial lining consisted of cuboidal cells, in three cases of cylindrical and in one of flat cells.

A Very Unusual Cyst occurring high up in the Vaginal Fornix.—Path. No. 1850 must, I think, be included under those probably arising from Gartner's duct on account of its location—the right vaginal fornix. It, however, presents a most unusual histological picture.

The cyst was 1 cm. in diameter with walls 5 mm. thick. Projecting from its inner surface were dome-shaped elevations fully 2 mm. in length (Fig. 19).

The vaginal mucosa over the cyst is atrophic but normal. The walls are composed of fibrous tissue. The dome-like elevations are newly formed, consisting of small, round cells and many young capillaries. This tissue is permeated by polymorphonuclear leucocytes. Just beneath the inner surface is a well-defined gland-like space lined with cylindrical epithelium.

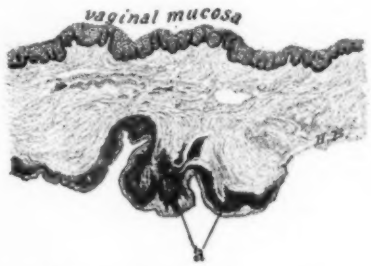

FIG. 19.—DOME-LIKE ELEVATIONS PROJECTING INTO A VAGINAL CYST (4 DIAMETERS).

Gyn.-Path. No. 1850. The cyst was situated in the right vaginal fornix. The vaginal mucosa over the cyst is normal. The walls are composed of ordinary connective tissue. Projecting into the cavity are the dome-shaped elevations *a*. These are composed of small round cells and young capillaries. For the character of the cyst lining see Fig. 20. Over these dome-like elevations are from 20 to 30 layers of squamous epithelium.

The lining of the cyst varies much in different places. Over the dome-shaped elevations are from two to twenty layers of squamous epithelium. At other points are definite finger-like folds with gland-like depressions between them (Fig. 20). The folds and the clefts between them are lined with one layer of cylindrical or cuboidal epithelium and have oval nuclei situated near the base of the cell. A slight inflammatory change is evident, as polymorphonuclear leucocytes and small round cells are seen between the epithelial cells

While this case is in all probability rightly classed with those having their origin from Gartner's duct, the histological picture is certainly difficult of explanation. This cyst gives no evidence whatever of malignancy. Such gland-like spaces may, however, account for the occasional primary adeno-carcinomata that develop in the vagina. In rare instances, as pointed out by Veit and mentioned elsewhere, Gartner's duct is patent all the way from the parovarium to the vagina. Cystic dilatation of the entire duct occasionally occurs, and as a result we have a vaginal cyst filled with clear fluid and extending up along the side of the uterus to the parovarium. This might well be termed a vagino-parovarial cyst. When of moderate size it will occupy one side of the vagina, but when very large, it will occupy not only the lateral wall but also encroach on the anterior and posterior surfaces of the vagina. The cyst contents are usually clear and watery, but if there has been hæmorrhage into the cavity, they are chocolate-colored. At times these cysts are only partially filled with fluid. Accordingly if pressure be exerted on the vaginal portion it collapses, the parovarial segment meantime becoming tense. On the other hand, if pressure be made over the parovarium, the tumor mass in this situation disappears and the vaginal portion becomes distended. In none of our cases did we find evidence of a patent Gartner's duct.

Vaginal Cysts arising from Urethral Glands.—If vaginal

FIG. 20.—EPITHELIAL LINING OF A VERY UNUSUAL VAGINAL CYST (50 DIAMETERS).

Gyn.-Path. No. 1850. This cyst was 1 cm. in diameter and situated in the right vaginal fornix; at *a* we have a lining of one layer of high cylindrical epithelium which at *b* seems to have proliferated resembling squamous epithelium. In the vicinity of *c* there are distant finger-like ingrowths lined with one layer of low cylindrical epithelium and at *d* there is a definite gland-like space. At *e* the cyst is lined with many layers of cells resembling squamous epithelium. A typical transition epithelial lining is seen at *f*,—a superficial layer of low cylindrical cells resting on several layers resembling squamous epithelium. The cyst walls show considerable inflammatory reaction, particularly noticeable at *g*.

cysts ever owe their origin to urethral glands, such a condition is of very rare occurrence. The possibility, however, cannot be excluded; in fact in two of our cases various histological appearances would justify the supposition that the tissue is very similar to, if not identical with, that of the urethra. In Path. No. 2870 we have a cyst, 1 x .5 cm., oval in form. The overlying vaginal mucosa is normal. The cyst walls are composed of fibrous tissue. The epithelial lin-

ing of the cyst presents a most unusual picture. It consists of from three to eight layers. The superficial layer is cylindrical and rests on the underlying layers of flattened and deeply staining cells. The general arrangement of the epithelium simulates that found in the urethra.

In Path. No. 1502 we have a cyst, 1 x 1.5 cm., in the anterior vaginal wall just within the hymen and to the right of the urethra. It is filled with clear fluid and has a delicate finger-like ingrowth. The cyst lining is composed of one layer of cylindrical ciliated epithelium (Fig. 21).

In the cyst wall is a definite gland-space lined with high cylindrical ciliated epithelium. It is just possible that in this case the cyst owes its origin to urethral elements. An origin from Gartner's duct can, however, equally well be claimed.

Although in both of these cases the features in the main would suggest their origin from urethral structures, the connecting link, namely the direct continuity with the urethra, is wanting.

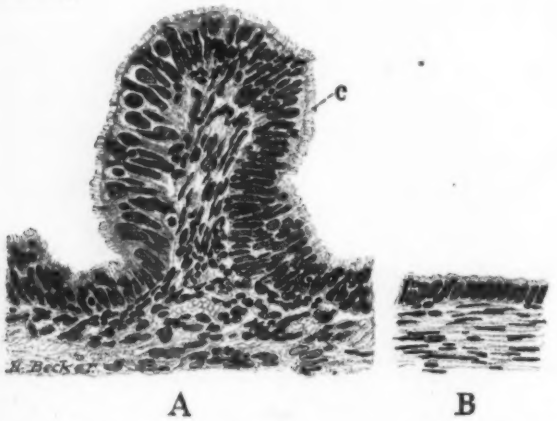

FIG. 21.—THE LINING OF A CYST SITUATED IN THE ANTERIOR VAGINAL WALL (400 DIAMETERS).

Gyn.-Path. No. 1502. *A* is the small projection, covered by cylindrical ciliated epithelium. The stem of the projection is formed by young connective tissue cells. *B* represents a small portion of the cyst wall. The cyst has been cut at right angles and we see that it is lined with a single layer of cylindrical cells.

Unclassified Vaginal Cysts.—In nine of our cases owing to lack of clinical details it was impossible to venture a classification with any degree of certainty. In Path. Nos. 1470, 4060, 5792, 6274, and 2442 little is known of the clinical history. Path. No. 955 looks very much like a cystic dilatation of Gartner's duct. The cavity was lined with one layer of cuboidal epithelium.

In Path. No. 2010 the small cyst had a finger-like ingrowth and was lined with one layer of cylindrical epithelium. It probably also represented a dilated segment of the duct. Path. No. 5037 appeared to have a similar origin.

In Path. No. 4079 B the small cyst was lined with one layer of cuboidal epithelium and lay in close contact with an inclusion cyst. In all probability it was a dilated vaginal gland.

Gas Cysts in the Vagina.—Various names, such as colpohyperplasia cystica and colpitis emphysematosa, have been applied to this affection, which has been accurately described by v. Winkel. This condition is usually associated with pregnancy and consists of small cystic dilatations occurring usually in the submucosa, but occasionally in the epithelium itself. On puncturing the cyst there is a report with the escape of gas and the cyst collapses. Such cysts only last for a short time and then disappear.

v. Winkel in 1886 reported three observations in pregnant women. In a space that could be covered by a dollar he found fifteen to twenty cysts. All were superficial and transparent. The mucosa in which these were embedded was hyperæmic and succulent and the cysts were filled with gas. On puncture there was a loud noise with an escape of gas. C. Braun in 1861 recorded similar instances. According to Eisenlohr the cause of this disease must be a gas-producing micro-organism which stretches the lymph vessels and forces the lymph and organisms into the surrounding tissue. According to Strauss, as quoted by Veit, the cysts were usually surrounded by connective tissue, rarely by epithelium. Their occurrence seems to be analogous to that of gas cysts in the liver and other organs, and we should not be surprised if in the near future Welch's *B. ærogenes capsulatus* should be proved to be the causative factor. No treatment is necessary, as the cysts are of short duration.

Echinococcus Cysts.—In countries in which the echinococcus is prevalent, cysts may develop in the tissue between the rectum and vagina. They may project into the vagina and resemble vaginal cysts. If a doubt as to their nature exists a careful microscopical examination of the cyst contents or of its wall will render the diagnosis clear.

Clinical History of Vaginal Cysts.—All of the cysts in our cases were relatively small, and naturally gave rise to no symptoms whatever. In fact they were detected during examinations for some other trouble, or, as in case of inclusion cysts, during operations for perineal tears. Undoubtedly many of the smaller cysts are overlooked as in the ordinary routine laboratory examinations we have found some of which no account had appeared in the clinical record. Cysts 6 to 8 cm. in diameter partially block up the vagina and may interfere with coitus. If situated in the posterior wall they may roll the pelvic floor out in such a manner that at first sight prolapsus of the vagina may be diagnosed.

Cysts of the posterior wall have, in a few instances, formed effectual barriers to delivery. In Peter's case, for example, the cyst contained about one pound of clear fluid, and had to be evacuated with the trocar before labor could proceed normally.

In the case of a vagino-parovarial cyst which is not full mere pressure is sufficient to remove the obstruction, the fluid passing up to the parovarium and the vaginal portion collapsing into a flaccid pouch.

Vaginal cysts in the posterior wall may have to be differentiated from an abscess in the recto-vaginal septum. The cysts are not tender. Abscesses are painful, of rapid develop-

ment, and are accompanied by fever. In the lateral wall a vaginal cyst may be mistaken for a blind vagina. The thick walls of the occluded and imperfectly developed vagina and the fact that the uterus is imperfectly developed will usually suffice to render the diagnosis clear.

A suburethral abscess may bear a striking resemblance to a vaginal cyst. In this case, however, pressure on the abscess will be followed by an escape of pus from the urethra and by collapse of the sac.

Treatment.—The smaller cysts are excised and the resultant cavity sutured. Where it is somewhat large and removal is difficult, half or three-quarters of the cyst, according to circumstances, may be cut off, and the edge of the vagina united with that of the cyst on all sides. The remaining portion of the cyst thus becomes a part of the vagina and gradually unfolds until it is scarcely recognized. Where the cyst is of the vagino-parovarial type drainage or a combined abdominal and vaginal removal is necessary. It is, however, seldom wise to resort to an abdominal operation, unless there are pressure symptoms or the cyst is very annoying. A small dilated blind ureter must always be borne in mind when removal of cysts in the lateral or anterior wall is contemplated.

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ANALYSIS OF VAGINAL CYSTS OBSERVED AT THE JOHNS HOPKINS HOSPITAL DURING THE PERIOD 1893 TO JANUARY 1, 1904.

[If the reader wishes further particulars about the drawings in the text they will in most instances be found in this tabulated list of the cases. For example, Fig. 1 is from Gyn. Path. No. 955; on referring to this table Gyn. Path. No. 955 is readily found in the first column; the chief clinical features of the case together with the gross and histologic appearances of the cyst are also given.]

Clinical No.	Age.	White or Black.	Para.	Perineal tear.	Previous perineal operation.	No. of cysts.	Site of cysts.	Size.	Shape.	Thickness of cyst wall.	Cyst contents.	Inner surface of cyst.	Condition of overlying vaginal mucosa.	Composition of cyst wall.	Epithelial lining of cyst	Cyst contents (microscopic).	Remarks.
3170	30	White.	2	Complete.	.....	..	.....	1.5 cm.	Irregular, globular.	.. ...	Creamy yellow.	....	Slight thickening with faint downgrowths.	Connective tissue.	Squamous epithelium, 5 to 30 layers.	.....	Negative on slide and culture.
3308	29	Black.	..	..	.....	1	Just beneath urethra and 2.5 cm. within vagina.	4.5x3.5 cm.	.....	1-2 mm.	Transparent.	Smooth and glistening.	Atrophied.	Connective tissue; rich blood supply; small round-cell infiltration beneath surface.	One layer of flat epithelium.		
3402	36	White.	7	Yes.	0	1	Ant. vaginal wall.	1.5 cm.	Globular.	1.5 mm.	Transparent.	Smooth and glistening.	Normal.	Fibrous tissue and non-striped muscle fibers.	One layer of cylindric epithelium.	.....	Stokes' drawing
236 San.	..	"	..	"	0	1	.....	6 mm.	Globular.	0.5 mm.	Transparent.	Smooth	Normal, thickening at one point.	Fibrous tissue; contains gland resembling cervical gland in lining and secretion; is surrounded by inflammatory zone.	One layer of cuboid epithelium.		

ANALYSIS OF VAGINAL CYSTS OBSERVED AT THE JOHNS HOPKINS HOSPITAL DURING THE PERIOD 1893 TO JANUARY 1, 1904.—*Continued.*

Gyn. Path. No.	Clinical No.	Age.	White or Black.	Para.	Perineal tear.	Previous perineal operation.	No. of cysts.	Site of cysts.	Size.	Shape.	Thickness of cyst wall.	Cyst contents.	Inner surface of cyst.	Condition of overlying vaginal mucosa.	Composition of cyst wall.	Epithelial lining of cyst.	Cyst contents (microscopic).	Remarks.
411	4834	36	"	6	"	Repaired in 1890.	..	.....	2.5 cm.	.....	2 mm.	....	....	Normal on sides, total absence over prominent part; no evidence of inflammation where epithelium is missing.	Fibrous tissue; considerable muscle; small round-cell infiltrat'n beneath cyst epithelium.	Several layers of squamous epithelium.	Swollen fatty epithelial cells, many polymorphonuclear leukocytes and small round cells.	Stokes' drawing
1470	4928	41	"	6	"	.....	1	.....	8 mm.	.....	.....	....	....	.....	.....	.....	.....	Details missing.
1502	4971	..	"	..	"	.....	2	Just within right vaginal wall in sulcus.	1x1.5 cm. 0.5 cm.	.....	.....	Clear fluid.	Very small, finger like ingrowth.	No vaginal mucosa.	Fibrous tissue; small gland in wall, lined by one layer of cylindric epithelium.	One layer of columnar cells.	Some desquamated epithelial cells; some cells filled with yellow chromatin droplets.	Stokes' drawing.
1504	4973	..	"	6	"	Repaired 3 yrs. ago.	1	Posterior wall near outlet.	2.2 cm.	.....	.....	Transparent fluid.	....	.....	Fibrous tissue; some small round cell infiltration of wall.	Squamous epithelium; in places 10 to 12 layers; where stroma is absent cells are swollen and filled with brown pigment.		
1518	4996	..	"	Yes.	Complete.	.....	1	Posterior just to right of median line.	2x1.5 cm.	Globular.	1 to 3 mm.	....	....	Atrophy over prominent part, normal on sides.	Fibrous tissue.	Squamous epithelium, 1 to 7 layers; in places low cuboid.		
562	....	..	....	..	..	.....	..	.....	.....	.....	.....	....	....	Normal.	Fibrous tissue.	One layer cuboid cells.		
776	Specimen.	..	White.	..	Yes.	.....	1	Anterior vaginal wall.	8x5 cm.	.....	3 mm.	....	....	Normal.	Fibrous tissue; convoluted cyst-wall lined by high cylindric epithelium; evidently due to downward projections of crypts.	One layer high cylindric; nucleus at base as in cells from cervix; in places cells cuboid; crypts present in walls.	.....	Stokes' drawing
789	San.	..	....	..	..	.....	1	Left vaginal wall.	1x2 cm.	.....	.....	....	Smooth and glistening.	Normal.	Fibrous tissue.	10 to 20 or more layers squamous epithelium.		
850	5400	29	White.	0, married.	No.	No.	1	Right side high up.	1 cm.	....	5 mm.	....	Dome-shaped elevation 2x2 mm.	Thickened but normal.	Thickened just beneath mounds; great small round-cell and polymorphonuclear infiltration with new capillaries, gland-like space lined by cylindric epithelium just beneath inner surface.	Over mounds lining of from 2 to 20 or more layers squamous epithelium; in places definite finger-like folds with gland-like depressions, one covered by a layer of perfectly cylindric epithelium; nuclei oval and near base; between epithelial cells, mono- and polymorphonuclear leukocytes.	Some polymorphonuclear leukocytes.	
910	Specimen.	..	....	..	..	.....	1	.....	5 mm.	...	1 mm.	....	....	Normal.	.....	One layer cuboid or low cylindric epithelium; small finger-like ingrowths covered by cylindric epithelium.	Desquamated epithelium.	

ANALYSIS OF VAGINAL CYSTS OBSERVED AT THE JOHNS HOPKINS HOSPITAL DURING THE PERIOD 1893 TO JANUARY 1, 1904.—*Continued.*

Clinical No.	Age.	White or Black.	Para.	Perineal tear.	Previous perineal operation.	No. of cysts.	Site of cysts.	Size.	Shape.	Thickness of cyst wall.	Cyst contents.	Inner surface of cyst.	Condition of overlying vaginal mucosa.	Composition of cyst wall.	Epithelial lining of cyst.	Cyst contents (microscopic).	Remarks.
6835	28	White.	1	Yes.	0	2	A, posterior r. side 2 cm. B, within vagina in scar tissue.	6 mm. 6 mm.	....	0.5-1 mm.	....	....	Normal.	Fibrous tissue.	A, 1 layer cuboid or almost flat. B, 3 to 20 layers squamous epithelium.		
6846	33	"	1	"	0	2	Posterior wall close to scar in sulcus.	....	....	....	....	....	Normal over both.	Fibrous tissue.	A, lined by several layers of squamous epithelium. B, apparently lined by cuboid epithelium.	Desquamated epithelium. Mucus.	
6850	29	"	1	"	0	1	Left vaginal fornix.	1 cm.	....	1.2 mm.	....	....	Thinned out over prominent part.	Fibrous tissue.	One layer cuboid epithelium.		
6287	35	"	3	"	0	1	Right vaginal fornix to right of cervix.	1x1.5 cm.	Globular.	1 mm.	Clear fluid.	Smooth	Normal	.....	One layer cylindric in places cuboid epithelium.		
6504	29	"	5	"	0	..	.....	5 mm.	Round.	....	....	....	...	Fibrous tissue.	Many layers squamous epithelium.	Partly filled with squamous epithelium.	
Specimen.	..	....	..	..	.....	..	.....	1 cm.	Globular.	0.3 mm.	....	....	Normal but atrophic.	Fibrous tissue along one side gathered into little folds.	One layer cylindric epithelium.		
6656	48	White.	1	Yes.	0	1	Right vaginal sulcus in scar.	1.5 cm.	...	....	....	Smooth	Normal.	.....	One layer very low, cuboid epithelium almost flat.	Mucus taking hematoxylin stain.	
6703	21	"	1	Complete.	0	2	.....	2 mm. 1 mm.	Globular, side by side.	....	....	Smooth	Normal.	Just beneath cyst epithelium non-striped muscle fibres.	Each cyst lined by one layer cuboid epithelium.		
6714	36	"	4	Yes.	0	..	.....	Embed'd 2 mm. in scar tissue.	Oval.	....	....	...	....	Just beneath epithelium of cyst dense area containing giant cells, some with nuclei in center, others in periphery; centers of some contain a faintly granular mass.	3 to 8 layers flattened squamous epithelium.	Desquam. and necrotic epithelium and irregular masses of granular material similar to that found in the giant cells.	
6787	40	"	6	"	0	..	.....	6 mm.	Globular.	2 mm.	....	....	Normal.	Fibrous tissue.	1 to 15 layers of squamous epithelium.		
6841	33	White.	1	Yes.	0	..	In right lateral wall.	1.4x1.1 cm.	Globular.	1 mm.	..	Smooth.	Gathered up into folds; deep layer pigmented.	Fibrous tissue.	1 layer cuboid or flat epithelium.		
6855	34	"	3	..	.....	1	Left lateral wall just within hymen.	3x1.4 cm.	Oval.	.....	....	Smooth.	Normal.	Just beneath cyst lining two small gland-like spaces lined by cylindric epithelium.	1 layer cuboid cells, apparently 2 to 3 layers in a few places.	Granular material taking hematoxylin stain.	Pearly white, covered on one side by squam. epithel.
6887	38	"	4	Yes.	0	1	Posterior vaginal wall.	3x2 cm.	.....	.....	....	....	Normal but atrophied over prominent part.	Fibrous tissue.	3 to 20 layers of squamous cells.		
7008	21	"	1	"	0	1	Left wall.	Cystic mass (of 3 cysts) 9 mm.	.....	0.2 mm.	....	Somewhat irregular.	Normal.	Slight projections of fibrous tissue into cyst cavities; walls between cysts exceedingly delicate.	2 to 3 layers of squamous epithelium.		

ANALYSIS OF VAGINAL CYSTS OBSERVED AT THE JOHNS HOPKINS HOSPITAL DURING THE PERIOD 1893 TO JANUARY 1, 1904.—*Continued.*

Clinical No.	Age.	White or Black.	Para.	Perineal tear.	Previous perineal operation.	No. of cysts.	Site of cysts.	Size.	Shape.	Thickness of cyst wall.	Cyst contents.	Inner surface of cyst.	Condition of overlying vaginal mucosa.	Composition of cyst wall.	Epithelial lining of cyst.	Cyst contents (microscopic).	Remarks.
7453	32	"	2	"	0	..	Embedded in scar tissue.	1.5 mm.	.....	.....	....	....	Depression from vagina 4 mm. into depth lined by partly macerated squamous epithelium only separated from cyst by 6 rows of connective tissue cells.	Fibrous tissue.	1 to 7 layers fairly well-defined squamous epithelium.	.....	Definite inclusive cyst.
7847	34	"	1	"	0	1	Post. wall near outlet embedded in fibrous tissue.	5 mm.	.....	.....	....	....	.....	.....	1 to 20 layers squamous epithelium.	.....	Desquam. epithelium, free granular material.
7804	35	"	4	"	0	1	Left lateral wall in scar.	3 mm.	Slightly irregular in outline	.....	....	....	.....	Dense fibrous tissue.	Apparently one layer of squamous cells.		
7835	26	"	3	"	0	2	.....	A, 4 mm. B, 3 mm.	.....	.....	A, yellow B, clear fluid.	....	Thinned out; groups of small round cells beneath surface epithelium.	Fibrous tissue; partition between cysts very delicate.	A, 1 to 4 layers of squamous cells. B, 1 layer cuboid cells.	A, desquamated epithelium + débris.	Interesting to find different kinds of cysts side by side.
7854	37	"	10	..	.....	..	.....	2 mm.	Round.	.....	....	....	.....	.....	2 to 20 or more layers squam. epith. cells stain more deeply than usual; a few polymorphonuclear leukocytes betw'n epithelial cells.	.....	Double vaginal septum removed.
8457	19	"	0	..	.....	1	Anterior vaginal wall just within hymen.	3x3x4 cm.	.....	1 mm.	Clear fluid.	....	Normal.	Fib. tissue; definite inner zone of non-striped muscle running parallel to cyst; beneath inner epithelium a definite stroma in places; cells are round or oval, have deeply staining nuclei, resemble stroma of uterine mucosa.	1 layer of cuboid or low cylindric epithelium clinging to inner surface.	A few mono- and polymorphonuclear leukocytes.	
San.	..	"	Yes.	Yes.	0	..	.....	3 mm.	.....	.....	....	....	.....	Fibrous tissue.	2 to 7 layers of squamous cells.		
8041	33	"	2	Complete.	0	..	.....	5x2 mm.	.....	2 mm.	....	....	Normal.	Fibrous tissue.	10 to 30 layers of squamous epithelium; superficial layers disintegrated.	Desquamated epithelium, débris, and large droplets, apparently fat.	
8844	33	"	3	..	.....	1	Ant. vaginal wall under urethra.	2.5x1.5 cm.	Ovoid.	0.2 mm.	....	Smooth.	Atrophic over prominence on sides thrown into long tongue-shaped folds.	Fibrous tissue, here and there infiltrated by clusters of small round cells.	1 layer of cuboid or almost flat cells.		
8846	60	White.	3	Yes.	0	..	.....	7x8 mm.	.....	.....	....	....	Normal.	Fibrous tissue.	1 layer of almost flat cells, cuboid type.		
8851	38	"	3	"	.....	..	.....	3 mm.	Round.	2 mm.	....	....	Normal.	Fibrous tissue within blood vessels.	2 to 7 layers of squamous epithelium.		

ANALYSIS OF VAGINAL CYSTS OBSERVED AT THE JOHNS HOPKINS HOSPITAL DURING THE PERIOD 1893 TO JANUARY 1, 1904.—*Continued.*

Clinical No.	Age.	White or Black.	Para.	Perineal tear.	Previous perineal operation.	No. of cysts.	Site of cysts.	Size.	Shape.	Thickness of cyst wall.	Cyst contents.	Inner surface of cyst.	Condition of overlying vaginal mucosa.	Composition of cyst wall.	Epithelial lining of cyst.	Cyst contents (microscopic).	Remarks.
1194 San.	..	"	Yes.	Yes.	.....	1	Posterior vaginal wall.	5 mm.	Round.	2 mm.	....	Smooth.	Normal.	Fibrous tissue.	3 to 8 layers of squamous epithelium.		
9028	31	"	1	"	.....	1	Posterior vaginal wall.	4 mm.	.....	.....	....	....	.....	.....	4 to 6 layers of squamous epithelium.	Filled with desquamated epithelium.	
San.	..	"	Yes.	"	.....	..	Posterior wall.	.....	.....	.....	....	....	Normal.	Fibrous sissue.	2 to 4 layers ill-defined squamous epithelium.	Granular detritus.	
9014	25	"	1	"	.....	1	In left posterior wall embedded in deep scar.	8 mm.	.....	.....	....	....	Atrophic but normal.	Fibrous tissue.	2 to 10 layers of squamous epithelium.		
San.	..	"	Yes.	Complete.	.....	2	.....	1 mm. 1.5 mm.	Round.	.....	...	....	Normal.	Fibrous tissue; small circular clumps of epithelium: near center two definite glands lined by cylindric epithelium.	Many layers squamous epithelium; polymorphonuclear leukocytes between epithelial cells.	Filled with desquammated epithelium and polymorphonuclear leukocytes.	Definite inclusion cyst, also well-defined vaginal glands.
9060	26	"	1	Complete.	.....	..	.....	5 mm.	.....	1 mm.	Clear fluid.	....	.....	Fibrous tissue.	Apparently cuboid or almost flat epithelium.		
9085	28	"	2	Complete.	.....	..	.....	3 mm.	Round.	.....	Yellow and opaque.	....	.....	Fibrous tissue.	3 to 10 layers of squamous epithelium; superficial layers degenerated—contain large vacuoles.		
9021	32	"	6	Complete.	.....	..	.....	1.5 mm.	Round.	3 mm.	Yellow and opaque.	....	Normal.	Fibrous tissue.	2 to 8 layers of squamous epithelium; superficial layers almost colorless; vacuolated.		
Specimen.	..	....	....	....	.....	..	.....	1 cm.	.....	1 mm.	....	....	.....	.....	Single layer columnar cells.		
San.	..	White.	Yes.	Complete.	.....	..	Lateral wall.	1 cm.	.....	2 mm.	..	Smooth.	Normal.	Fibrous tissue; contains irregular gland-like spaces lined by very high cylindric epithelium secreting mucus; most of glands open into 1 cavity.	1 layer of high cylindric epithelium and a few gland-like spaces at irregular intervals just beneath cyst cavity.	.....	May have developed from urethral glands or Skene's ducts.
San.	..	"	Yes.	Yes.	.....	..	.....	1 cm.	Round.	2 mm.	....	....	Normal.	Fibrous tissue.	1 to 15 layers degenerated squamous epithelium.	Partially filled with desquamated epith. and crystals.	
4118	35	"	2	"	.....	1	Ant. vaginal wall under urethra.	3.5x2.5x2 cm.	.....	.....	Clear yellow.	....	Normal.	.....	1 layer columnar or cuboid cells.		
Specimen.	..	....	...	....	.....	..	.....	.....	.....	.....	....	....	Normal.	.....	1 layer columnar epithelium; oval nuclei near bottom of cell; protoplasm takes hematoxylin stain.		
Specimen.	..	....	....	....	.....	1	.....	1x0.5 cm.	Oval.	.....	....	....	Normal.	Fibrous tissue.	Remarkable picture 3-8 or 9 layers, the superfic. layer high cylindric resting on flattened deeply staining cells; the cylindric cells bear resemblance to cervical epithelium.		

THE ETIOLOGY AND PATHOGENESIS OF PERNICIOUS ANÆMIA.[1]

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The problem presented for solution by progressive pernicious anæmia is one of considerable difficulty, and to this difficulty there are many contributing factors. The general features of the disease offer scarcely a hint to one in search of the causal factor or factors. The malady is widely distributed geographically with few local variations in prevalence except that in Switzerland, and especially in the vicinity of Zürich, it is reported to occur more frequently than elsewhere, which may be due in part to the unusual interest in the disease which was aroused in that locality by the work of Biermer, Gusserow, and Eichhorst. On the other hand it is claimed that Munich and Prag enjoy a relative immunity. There is no racial peculiarity of distribution, and while most of the cases reported are from among the white races, as would be expected, in McCrae's series of 40 cases from Dr. Osler's wards at the Johns Hopkins Hospital, there are two negroes.

As to sex, there is some disagreement in statistics. In Germany it is commonly taught that there is a greater prevalence among women, an assertion which is based on such series as those of Ehrlich, showing 130 women to 110 men, and of Lazarus, from the Berlin hospitals, of 172 women to 102 men. In England and in the United States, with perhaps more rigid criteria of diagnosis, the majority of the cases are in the male sex. Of Cabot's 50 cases, 33 were males; of McCrae's 40, 32 were males; Hunter reports 19 cases in men, 6 in women, and Colman reports in a series of cases, analyzed by him, 60 males and 27 females. From the tabulation of a number of series of reported cases Colman found 323 males and 227 females, and calls attention to the fact that while in earlier statistics women predominate, in the later, men are decidedly more numerous.

Though affecting people at the extremes of life, the disease is of the greatest frequency in those of middle age. The majority of Lazarus' cases fell in the third and fourth decades. McCrae and Cabot find the disease is most frequent in the fifth decade; Colman, between the 35th and 45th years. Monti and Berggrün have collected from literature 16 cases under 15 years of age, and both Cabot and Lazarus report two cases in the eighth decade.

The patients affected are said to be more often of the robust habit than otherwise. Occupation seems to bear no causal relation, nor mode of life. Although the earlier opinion seems to have been that pernicious anæmia was chiefly a disease of the poorer classes, the later view, as expressed by Lazarus, is that the proportion of cases among the well-to-do is above the ratio of the well-to-do to the poorer class. In a few cases a family tendency to the disease is suggested.

In a search for more immediate causes, one is confronted by another difficulty in the very nature of the disease. One is dealing with a chronic disease and one of so insidious an onset that the patient comes to the attention of the physician only when the process is well advanced and the patient himself is unable to tell definitely when it began, and what were the contributing causes. A good percentage of cases can give a history of no contributing factors, but a large number of severe, progressive, and fatal anæmias have followed events or have been associated with lesions well recognized as giving rise to anæmias of a secondary type. This has raised the question as to whether these lesions are to be considered as causal factors of the pernicious anæmia or as associated conditions; and if they be accepted as the causal factors, are we to group together the whole series, those anæmias with apparent causes and those without, as representing a symptom complex, a clinical picture presented by all serious anæmias, or are we to separate the anæmias without apparent adequate cause from the other group, as a distinct clinical entity? The question is as old as the two classical descriptions of the disease, that of Addison, published in his monograph on Disease of the Suprarenal Capsules in 1855, and that of Biermer, published in 1872; and one can perhaps best arrive at our present conception by reference to those two papers.

Addison described a "very remarkable form of general anæmia occurring without any discoverable cause whatever; cases in which there had been no previous loss of blood, no exhausting diarrhœa, no chlorosis, no purpura, no renal, splenic or miasmic, glandular, strumous, or malignant disease. Accordingly in speaking of this form in clinical lectures, I perhaps with little propriety applied to it the term 'idiopathic' to distinguish it from the cases in which there existed more or less evidence of some of the usual causes or concomitants of the anæmic state. The disease presented in every instance the same general character, pursued a similar course, and with scarcely a single exception was followed after a variable period by the same fatal result. It occurs in both sexes, generally, but not exclusively beyond the middle period of life, and so far as I at present know, chiefly in persons of a somewhat bulky frame and with a strongly marked tendency to the formation of fat. . . . On examining the bodies of such patients after death, I have failed to discover any organic lesion that could properly or reasonably be assigned as an adequate cause of such serious consequences."

Biermer in 1872 reported 15 cases of anæmia occurring between the ages of 18 and 52 years with the symptoms of a

[1] Paper read before the Medical and Chirurgical Faculty of Maryland, December 16, 1904.

progressive pernicious anæmia, and which he concluded were caused by insufficient and unsuitable nourishment, unhygienic dwellings, exhausting discharges, in particular long-continued diarrhœa, and also, at times, by diseases accompanied by hæmorrhages, including in a common group anæmias with these causal factors and those with undiscovered cause.

These two views express practically the division that exists to-day among the clinicians on the subject, the Germans adhering to the Biermer view, while the English and American authorities are inclined to accept Addison's. It would lead too far afield to quote fully the expressions of opinion on the matter. Let two quotations suffice.

William Hunter, possibly an extremist on the one side, maintains: "The anæmia which Addison described is really a remarkable infective disease with definite antecedents, mode of origin, infective and hæmolytic lesions and clinical course. On the other hand, the investigations which have made this clear have also made clear that the condition described by Biermer is as its supporters truly maintain 'not a disease *sui generis*, but a frequently recurring group of symptoms met with in very different conditions of disease,' 'not an etiological unity, but only a symptomatic group which can be produced by causes of all kinds'; the most common cause being, as I hope to show, septic infection, this being the feature that has led them to be confounded with Addison's Anæmia."

On the other hand, Grawitz, among others, maintains that "the etiology of the symptom picture of pernicious anæmia is not uniform, many influences playing a part," and "the diseases showing this symptom-picture bear even as little relation to each other as do the members of other groups of diseases which have, as a striking feature, albuminuria or glycosuria."

The pathological conditions which have been regarded as bearing a causal relation to severe progressive anæmias is an extensive one. It includes, according to Stockman:

Pregnancy (Gusserow and many others).

Severe or protracted hæmorrhages (Habershon, Quincke, Schepelern, Finny, Greenhow, Stockman).

Gastric atrophy (Fenwick, Brabazon, Nothnagel, Henry, and Osler).

Typhoid fever (Rosenstein).

Syphilis (Mueller, Laache).

Yellow fever (Bramwell).

Mental shock (Mackenzie, Cortin).

Chlorosis (Mueller, Hall, Coupland).

Malnutrition.

Jaundice.

Sarcoma and carcinoma involving the marrow (Mosler and Gast, Grawitz).

Carcinoma of stomach (Nothnagel, Eisenlohr).

Intestinal parasites—Ankylostoma and Bothriocephalus (Schauman, Sahli, Leichtenstern).

These are all conditions, which if associated with anæmia, are, in the great majority of cases, accompanied by an anæmia of the secondary or chlorotic type. It seems probable in some of the reported cases that severe anæmias of the secondary type have been diagnosed progressive pernicious anæmia. For example, as to the causal part played by pregnancy, Lazarus notes that in recent years far fewer cases of pernicious anæmia following pregnancy are reported than in earlier years before the criteria for the diagnosis of pernicious anæmia were well established. He quotes Ahlfeld to the effect that he has never seen a case following pregnancy in his obstetrical practice. Such is also the experience of J. Whitridge Williams.[2] This may account for the change in the ratio of sexes affected, already noted as shown by Colman's statistics. Granting however, as one must, the occasional occurrence of these two conditions in the same patient, are we to ascribe to pregnancy a causal relation? In a chronic disease, which, when well established, may extend over three or four years of the patient's life during the child-bearing period, is it not more rational to look at the association of the two conditions as a coincidence,—the occurrence of a physiological event during the unrecognized state of anæmia? Or where causal relation seems indisputable, must not one look for some other factor to explain why this normal event in a woman's life should very exceptionally be followed by pernicious anæmia? In this light the improvement in obstetrical technique and the lessened number of cases of puerperal infection may account for the diminution in the number of cases of anæmia following pregnancy noted by Lazarus and others, and if such prove the case, it would tend to confirm Hunter's theory as to the real causal factor in such cases.

Certain of these arguments seem applicable to other conditions mentioned. Few would accept, for example, the case reported by Stockman following hæmorrhage, in which the red-blood corpuscles were reduced to one-fifth their normal number and the hæmoglobin to one-tenth its normal percentage, as giving the blood picture of pernicious anæmia—but rather as showing a severe secondary anæmia.

Jaundice is clearly to be regarded as a symptom, not a cause.

Gastric atrophy seems to occupy a different relation to pernicious anæmia than the conditions just discussed. Only a small percentage of cases of achylia gastrica and gastric atrophy present the picture of pernicious anæmia. A considerable number of cases of pernicious anæmia show gastric lesions which may be considered as early stages of a chronic inflammation, the result of which would be gastric atrophy. Some cases show complete atrophy of the gastric mucosa. Under such conditions one is not justified in ascribing a causal rôle either to the anæmia or to the gastric lesion. In some cases the symptoms of the gastric atrophy manifest themselves before the anæmia, in others not until considerably afterward, in still others, practically simultaneously, a time relation quite similar, as is noted by Faber and Bloch, to that presented by the spinal cord symptoms in pernicious anæmia; and the opinion of these authorities and of the majority of

[2] Personal communication.

recent writers on the subject is, that one must look at the blood lesion, the gastric lesion, and the cord lesion, as due to a common cause, and thus all features of the disease, pernicious anæmia.

The parasite Ankylostoma (Uncinaria) is generally assumed to produce an anæmia by abstracting blood from the intestinal walls, and in the great majority of cases it produces an anæmia of the secondary type. Thus Rogers in 1900, in reporting on uncinariasis in Assam, quotes Sandwith of Cairo, as reporting "in 173 cases of Ankylostomiasis, the percentage of hæmoglobin to be reduced nearly twice as much as that of the red-blood cells so that the color index was reduced to about one-half, just as it was in my own (Rogers) cases, allowing for the abnormally low hæmoglobin-value of healthy Assamese." It seems probable then that in cases where the picture of pernicious anæmia follows infection with these parasites, some further factor is to be sought.

Bothriocephalus latus, on the other hand produces an anæmia which is accepted by Lazarus, among others, as a pure picture of pernicious anæmia, and the parasite is regarded by him as the only positively recognized cause of the condition. The experiments of Schaumann and Talquist have shown that a substance may be extracted from the worms which is actively hæmolytic and this has led to some theorizing as to the pathogenesis of pernicious anæmia, to be referred to later.

Although some of the severe anæmias in literature may thus be excluded from the pernicious anæmia group, by rigid application of the diagnostic criteria—and although some supposed causal factors are apparently associated lesions, there are still cases following conditions, the well-recognized causes of secondary anæmias, which present the picture of pernicious anæmia. As to these in the present state of our knowledge of pernicious anæmia it seems impossible to say whether we are to assume that in some stage, any severe secondary anæmia may give the picture of pernicious anæmia or whether we may expect to find a common, as yet undiscovered cause for both the "idiopathic" group and the "symptomatic." However that question may be decided, one seems justified in assuming that the so-called "idiopathic" cases which show such uniform symptoms and blood findings, so similar a course and termination are entitled to a position as a clinical entity and that one may hope to find for them a single cause—and this disease we may define in Cabot's words, with a slight modification, as a profound and almost invariably fatal anæmia without adequate known cause, characterized by an extreme diminution in the number of red-blood cells and usually by other changes in the blood, indicative of a pathological mode of blood formation, as well as absence of emaciation and a tendency to spontaneous temporary improvement followed by relapse.

This position is arrived at, however, from a clinical rather than from a pathological standpoint. The pathological picture is, in general, one that might be expected as a result of a profound anæmia. The common findings are a lemon-tinted skin, well preserved adipose tissue, often of a brilliant yellow color; bright-red muscles; as a rule, an excessive amount of usually fluid, watery blood with soft clots; a serum which may have a tint as if bile-stained; extreme anæmia of all organs; marked fatty degeneration of the heart; frequently general petechial, subserous, submucous, and retinal hæmorrhages; a spleen of variable size, seldom very large; prominent hæmolymph glands; a pigmented kidney. The fatty marrow of the long bones is usually replaced by a greyish-pink or red, rather firm marrow; but exceptionally the fatty marrow persists and even replaces the red marrow of the cancellous bone near the epiphyses and in the ribs.

The microscopical examination adds little save that it shows in the spleen, and especially in the epithelial cells of the liver and kidneys, an excess of fine, yellowish granules which give the reaction for free iron. In the liver this pigment is pretty generally distributed in the lobule, but most heavily toward the periphery, where it is arranged in the cells in rows, surrounding the bile capillaries. In the kidney it lies in the tubules of the secreting type, perhaps especially in the ascending loops of Henle.

The marrow shows a picture not usually seen in actively regenerating marrow. One misses the preponderance of erythrocytes and normoblasts usually present and finds, instead, that the more frequent cell of the erythroblastic group is of the megaloblastic type. This was noted first by Cohnheim who called attention to its resemblance to embryonic marrow and suggested that it might be considered a reversion of the marrow to the youthful or embryonic type. Ehrlich designates the condition a "metaplasia."

In a certain percentage of cases, there are also spinal cord lesions, consisting of bilateral and usually symmetrical areas of degeneration and sclerosis confined chiefly to the posterior columns and the postero-lateral region, and in other cases, foci of degeneration about small vessels. There seems to be some question here, as to whether the more extensive changes are to be considered as a system disease, or as the result of the fusion of the focal lesions.

Likewise, in many cases there are demonstrable in the mucosa of the stomach lesions of a chronic type, varying from fatty degeneration of the tubules with increased, small, round-cell infiltration of the interstitial tissue to complete atrophy and sclerosis of the mucous membrane. Hunter calls attention to further lesions of an infectious type in the gastro-intestinal tract, in particular, a deep-seated inflammation of the tongue.

Such, in brief, are the general etiological factors and pathological findings. How are they to be interpreted in an effort to ascertain the cause and the pathogenesis of the disease?

In the first place it does not seem necessary to assume any specific predisposition to anæmia—at least not a predisposition with a pathological condition of the marrow as a basis. There is, however, a disproportion between the resisting power of the individual and the strength of the pathological agent producing the anæmic state—a disproportion shown by an

inability of the bone marrow to generate a sufficient number of red-blood cells to supply the deficiency. This disproportion is especially marked in the so-called "aplastic" cases, in which after death the marrow is found to be fatty and with practically no sign of regeneration. Whether this variability in reaction depends entirely on a variation in the intensity of the toxic agent or in part on the condition of the individual is the same problem as is presented in many diseases, as for example the variable resistance offered to invasion by the tubercle bacillus, or to the toxic agents producing a nephritis or a cirrhosis of the liver. It would seem to depend more on a general lack of resistance on the part of the individual than to any special predisposition or weakness of the bone marrow.

It is obvious that an anæmia may be produced in several ways: First, by insufficient or defective blood formation; second, by excessive loss of red-blood cells from the circulation, third, by excessive destruction of red cells; or, fourth, by a combination of the preceding factors or any two of them.

The picture of pernicious anæmia gives some evidence of the operation of each of these factors, and it is according to the emphasis placed on any one, that one must group the attempted explanations of the pathogenesis of the disease. It is not possible to give fully all of the theories as to causation in this paper, and a few selections must suffice.

Since Cohnheim in 1876 noted the hyperplastic condition of the bone marrow and especially the presence of the large, nucleated red cells of the megaloblastic type, and more especially since Ehrlich in 1880 called attention to the presence of the megalocytes and megaloblasts in the blood, the cause of the disease has been sought in the marrow, and there is a considerable group of supporters of the theory that this reversion of the bone marrow to an embryonic type is the primary lesion. Such was Cohnheim's idea.

In a recent paper Bloch adheres closely to this view, expressing the opinion that "Biermer's anæmia rests almost always on an asthenic condition of the hæmopoietic system, usually congenital, as a result of which the red-blood cells are insufficient for their function, or of a more unstable structure (chemical and physical), and therefore less resistant to injurious agents. All causal factors, to which the disease is often ascribed, are to be considered simply as accidental, exciting causes. . . . . It is a chronic disease, or better expressed, the establishment of the clinical picture, of which the characteristic lesion is a transformation of the bone marrow into a megaloblastic, embryonic type, requires a long time."

Houston says: "The changes found in the bone marrow in cases of progressive anæmia are an essential lesion of the disease directly accounting for the condition of the blood, and not, as some have supposed, of a secondary nature, the result of a severe anæmia."

Grawitz is probably to be included in this group as he recognizes two factors in pernicious anæmia, an individual predisposition and a pathological method of hæmopoiesis, his contention being that "the principal difference between pernicious and other severe anæmias lies not so much in the blood findings or not so much in the differences in the etiological moment as in the clinical course, the characteristic being that the progress of the anæmia is not checked, after removal of the cause, by a regenerative process in the hæmopoietic organs, but that after the removal of the cause, the blood formation proceeds in a faulty manner, producing an insufficient number of pathological cells."

William Pepper believed also in a deficiency in blood formation, designating the condition an "anæmatosis."

Stockman is the only recent writer who lays great stress on the part played by hæmorrhages in pernicious anæmia, yet, as has been previously noted, I think one must disagree somewhat with his interpretation of what constitutes the blood picture of anæmia, as well as with his dictum that pernicious anæmia is "simply a collection of symptoms characteristic of the highest degree of anæmia." He holds, as to the pathogenesis of the condition, that it is due to the following factors:

First, it follows on well-recognized debilitating causes.

Second, degenerative changes take place in the whole vascular system and these permit the occurrence of

Third, minute capillary internal bleedings, more rarely of external ones also, and that a persistent continuance of these leads ultimately to excessive anæmia and death.

Since the discovery by Quincke in 1877 of the excessive amount of iron in the liver of pernicious anæmia patients, its confirmation by Peters, and by the careful analyses of Hunter, together with the finding of iron-containing pigment in the kidney, and the determination of an excessive excretion of hydrobilirubin by the kidneys, an excess shown to increase during the exacerbations of the disease, diminishing again during periods of improvement (Hunter), as well as the determination of hæmoglobin and hydrobilirubin in the plasma of the circulating blood (Syllaba), sufficient evidence seems to have collected to show that if not the essential process, at least a major factor in the disease is the destruction of red-blood cells, a hæmolysis. There is no stronger advocate of this theory than William Hunter, who has also gone further than others in outlining a theory of the causation of the disease. He points out that in analyses of seven cases of pernicious anæmia, the liver and kidney contained 360 milligrams of iron per 100 gm. of dried organ substance, and the spleen, but 125 milligrams, while in seven cases of secondary anæmia, the spleen contained 362 milligrams and the liver and kidneys but 79. He lays great stress on this reversal of conditions in the two varieties of anæmias, and interprets it as indicating an excessive destruction of red-blood cells occurring in the field of the portal circulation and due to a toxin elaborated in the intestine. In 227 out of 273 cases of pernicious anæmia, or 83%, there were severe gastro-intestinal symptoms. Pathologically in a large percentage of his own cases, he records the presence of infective lesions in the gastro-intestinal tract either a "glossitis" of specific char-

acter or other forms of oral, gastric, or intestinal sepsis. As a result he concludes pernicious anæmia is a chronic infectious disease localized in the alimentary tract, caused by a definite infection of certain of its parts, chiefly of the stomach, occasionally also of the mouth and intestine. It is characterized by intermittent destruction of red-blood cells, by periodic disturbance of the alimentary tract, by occasional toxæmic attacks characterized by fever, sweats, and general nervous symptoms. Hunter's theory disregards the alterations in the bone marrow which are seen in pernicious anæmia, and it seems to fall short of a complete explanation not only in that respect, but also in this that, while he does not consider hæmorrhage to be a causal factor in the production of the disease, he does lay great stress upon the causal relation of a destruction of red cells in one field of the circulation—which to the whole system is but the equivalent of an internal hæmorrhage.

The Ehrlich-Lazarus theory recognizes the probability of the presence of some hæmolytic substance, calling attention to the bothriocephalus anæmias in which it has been shown that a hæmolytic substance is produced by the parasite. They assert that it is not necessary to assume a pre-existing abnormal marrow, but that all anæmia-producing influences stimulate the marrow to hyperplasia; that too long or too intense stimulation leads to the production of a megaloblastic marrow; that the capability of the marrow to react to stimulation is limited. Moreover, the difference in reaction between the normoblastic type of marrow and the megaloblastic may rest on a qualitative rather than a quantitative difference in stimuli—that there are stimuli of moderate intensity, but of special character which may cause the megaloblastic reaction as in bothriocephalus disease. They conclude that the anomaly of blood formation and the increased blood destruction are coördinate results of the same cause. "This cause," says Lazarus, "inasmuch as we have no other explanation for the megaloblastic transformation of the marrow than the presence of some toxic substance, we will assume to be the formation of toxins which have the capability of influencing the marrow in this specific manner."

To the mind of the writer, this latter theory approaches most closely the true solution of the question of pathogenesis—that of the absorption of a toxic substance, probably of intestinal origin, which acts on the circulating blood producing hæmolysis and through the circulation also on the marrow, resulting in a faulty hyperplasia. That this toxin is a result of gastro-intestinal infection as suggested by Hunter seems not improbable. There are other evidences of a toxic substance circulating in the blood—notably, the symmetrical lesions found at times in the spinal cord, which practically all investigators agree are the result of a toxin, and not of the anæmia *per se* as they are not found in even the severest types of secondary anæmia. According to Minnich, they resemble the lesions of Ergotism, Pellagra, and Lathyrismus. The atrophy and degeneration of the gastric tubules may possibly be atributed to the action of a circulating poison, if not due to an inflammatory process. Finally, in the multiple capillary hæmorrhages, quite resembling the hæmorrhages with such intoxications as those due to snake venoms where they are, according to Flexner, the result of an endotheliolytic principle or "hæmorrhagin," one has evidence of further toxic action.

This leaves unsettled the question of the nature of the toxin and of its mode of action on the bone marrow to produce its effect. While the writer recognizes the danger of drawing conclusions as to human pathology from animal experimentation and observation, certain findings in such experimental work seems to indicate a possible answer to the question. While studying the effects of artificial myelotoxic sera on the bone marrow of rabbits, the author became convinced that the statement of Ehrlich that megaloblasts are not a normal constituent of the adult bone marrow is an error, at least as far as the rabbit is concerned. Further search showed cells of the megaloblastic type in the marrow of all the common laboratory animals as well as in human marrow—a finding in agreement with the views of Engel, Pappenheim, and others. From this study it seemed certain, also, that there was a definite arrangement of both the leucocytic and erythrocytic cells of the marrow in nests and groups, and of the erythrogenetic groups, as expressed at that time,[1] the megaloblasts formed the proliferating center, corresponding to the position held by the myelocytes in the leucogenetic centers. Peripherally to the megaloblasts were found nucleated red cells of a smaller type, but with vesicular nuclei; with these and outside, normoblasts with pyknotic nuclei, and, at the extreme periphery mature red cells. In actively regenerating marrows mitotic figures were frequent in cells of the megaloblast size and type, and were occasionally found in smaller cells of the intermediate type. The normal mode of development of the red cell, then, seems to be as follows: A division of the megaloblastic cell produces either its like or a smaller cell, that called by the clinicians the "intermediate" nucleated red corpuscle. By reproduction of these, the normoblast results, while by a still further change, the absorption of the pyknotic nucleus, the mature non-nucleated red cell develops. This differs in no essential, except as to the fate of the nucleus, from the description given by Howell of the process of blood formation in the cat. This theory assumes that the division of the megaloblasts gives rise to cells differing in size and slightly in type from their ancestors—a condition paralleled probably in the lymph glands where in cases of hyperplasia, mitoses are found most numerously in the large cells of the germinative center. Outside of the hæmopoietic system, a similar process is seen in the tubules of the testicle, where the outer cells or spermatogonia differ from their descendants, the spermatocysts, and these again from the products of their division, the spermatoblasts.

As a result of this grouping of the erythrogenetic cells, the older and more mature red cells are constantly pushed toward the periphery by the division of the cells at the center, and

[1] Univ. of Penn. Med. Bulletin, July, Aug., 1903.

thus the non-nucleated red cell comes to lie farthest away and nearest the capillaries. In like manner it may be observed that the polymorphonuclear cells occupy the periphery of the leucogenetic groups lying nearest the capillary wall; and thus it is that on stimulation the marrow is able to respond with mature red and white cells.

More recent experiments show that the reaction of the marrow to different stimuli differs, depending upon whether the stimulus acts on the red cells of the circulation as in the case of a hæmorrhage or its equivalent, the destruction of red corpuscles in the peripheral vessels or upon the marrow itself as in the presence of a circulating toxin.

Let me quote one experiment illustrative of the reaction of the marrow to hæmorrhage and the blood picture resulting: A rabbit was bled from the ear-veins daily with a few exceptions for 18 days, the daily amount of blood extracted varying from 2-20 cc., the total amount being 184 cc., an average of practically 10 cc. per day. Daily complete and differential counts of the blood were made just before each bleeding and on one occasion, two hours afterward. As a result of the hæmorrhages the red corpuscles were reduced from a total of 5,988,000 cells per cu. mm. on the first day to 2,486,000 on the 19th day when the animal was killed. In none of the counts 24 hours after bleeding was there found a large number of nucleated cells; the highest number was 16 cells of the normoblastic type to the cu. mm. In the count two hours after the bleeding 108 normoblasts were found per cu. mm., the percentage being estimated from the number of such cells seen while counting 500 leucocytes, a method of approximate accuracy. Postmortem, the marrow showed the usual hyperplastic picture—the normoblasts being the predominant nucleated red cells.

In another rabbit, where 45 cc. of blood were taken at one bleeding and 27 cc. on the next day, the red count being reduced from about 7,000,000 to 2,592,000, there were as few nucleated red cells seen as in the previous case,—but 12 normoblasts per cu. mm. the first day and none the second.

Experiments with myelotoxic and hæmolytic sera give an entirely different reaction. In one dog which received intravenously 3.5 cc. of serum of a rabbit immunized against dog's red corpuscles, there were present in the circulating blood 24 hours later 900 nucleated red cells of the normoblastic type and 120 of the megaloblastic variety; at the end of 48 hours the number was approximately the same, the normoblasts numbering 928, and the megaloblasts 64; at 72 hours there were 500 normoblasts and no megaloblasts. The animal was not followed further.

On account of greater ease in manipulating and standardizing the toxin, the later experiments have been performed with ricin, a soluble toxalbumin from the castor oil bean, which has marked toxic action for leucocytes and red-blood cells in the rabbit. The hæmolytic action is shown by numerical reduction in red cells, by hæmoglobinuria and by deposits of pigment in spleen and lymph glands. The blood picture is quite uniform. One animal which had received a lethal dose of ricin intravenously showed, 24 hours afterward, 1130 normoblasts, 603 naked pyknotic red-cell nuclei, and 335 megaloblasts per cu. mm.

A second animal which had received a smaller dose showed, a day later, 1120 normoblasts and 875 naked red-cell nuclei, but no megaloblasts, with a reduction of 1,500,000 cells per cu. mm. in the total red count. On repeating the dose and waiting 8 hours, there were found 3472 normoblasts, 2884 naked nuclei, and 400 megaloblasts per cu. mm. The animal died during the second day.

Following smaller doses, and becoming marked when, after the reduction in red cells, the regeneration begins, the blood picture is quite suggestive of that seen in the pernicious anæmia. There are scattered nucleated red cells, the non-nucleated corpuscles show great variation in size, large cells or macrocytes being numerous; there is a slight tendency to poikilocytosis. After lethal doses the marrow itself gives direct evidence of the effect of the toxin in the presence of cells with pyknotic and fragmented nuclei and in minute hæmorrhages.

The conclusions I would draw from these experiments, which are still in progress, is that in hæmorrhage there is created a deficiency in circulating red cells, which is met by the marrow with the mature red cells lying close to the capillaries at the periphery of the erythrogenetic groups. In large hæmorrhages with exhaustion of the supply of mature red cells a certain number of normoblasts are called out to supply the deficiency.

On the other hand, with a circulating toxin, there is destruction not only of red cells in the circulation, but also of some, at least, in the marrow, even of normoblasts as suggested by the large number of naked nuclei found later in the circulation. The marrow responds, in this emergency, with nucleated red cells of normoblastic or megaloblastic type, depending upon the extent of the destruction. The experiment of the repeated dose of ricin where megaloblasts appeared only after the second dose would seem to confirm this idea, as well as the observations as to the arrangement of the cells in the erythrogenetic groups in the marrow.

Applying these conclusions to pernicious anæmia, it seems possible that an analagous toxin may be present, destroying red cells both in the circulation and in the marrow so that in the reaction, nucleated red cells are used to supply the deficiency—that further action of the toxin reduces the erythrogenetic groups more or less to the megaloblastic centers, diminishing greatly the regenerating power of the marrow and resulting in a discharge of megaloblastic cells in the hasty effort to supply the needs of the circulation. Thus, the regular orderly development of the groups of the marrow cells is interfered with and a short cut is taken from the megaloblast to the macrocyte, an imperfect, immature cell, as shown by its polychromatophilia and granular basophilia. In this light it is not difficult to see why cases of pernicious anæmia with few normoblasts, and more megaloblasts in the circulation are of graver prognosis than those with a large number

of normoblasts, and few megaloblasts. And again if one regard the presence of nucleated cells in the circulation as evidence of injury to the bone marrow, one has an explanation for the "nucleated red cells crises" of pernicious anæmia and leukæmia in which the blood picture resembles much that shown in ricin intoxication.

These observations and deductions seem to the writer to offer a not unsatisfactory explanation of the so-called reversion of the marrow to the embryonic type in pernicious anæmia.

Indebtedness is acknowledged to the following articles:

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RECURRING PHLEBITIS OF OBSCURE ORIGIN.

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There is a variety of phlebitis, affecting the veins of the extremities, and occurring in the absence of all conditions that are commonly recognized as predisposing to inflammation of the veins, which has attracted little or no attention from systematic writers. The cases, though apparently rare, are so similar in the essentials of their clinical course, and show so many striking and constant features in common, that they deserve for the present at least to be put together in a group by themselves, and to be sharply separated from other forms of acute venous inflammation. Clinically characterized by a progressive and relapsing course, they are obscure alike in their pathology and in their remote and immediate etiology. So consistent is the clinical picture which they present, that we may fairly consider them all, in our ignorance as to their more intimate nature, under the title of *idiopathic recurrent thrombo-phlebitis*. It is not asserted that the symptom-complex is a new one, for every one will recognize in the cases to be reported the main features emphasized by Paget, Prescott, Hewett, Tuckwell, Lancereaux, and others, as characteristic of the phlebitis associated with gout. But the present cases seem on the most careful consideration to be as certainly not dependent on this dyscrasia, as they are free from suspicion of a septic or traumatic origin. They are as remarkable for their apparent spontaneity as they are for the practical identity of their clinical details. It may be that we are not dealing with a new clinical group—it is even highly probable that we may be able eventually to refer these apparently mysterious cases to a variety of different causes. All that I shall attempt to show is that there occur cases of thrombo-phlebitis, with very individual and constant symptomatic features, yet differing from other forms of the affection, and with causes as yet absolutely unknown.

Case I. *Spontaneous thrombosis of the left internal saphenous vein* in a young man twenty-three years old. F. H. clear of gout and rheumatism, or other dyscrasia. Perhaps an unusually large proportion of his ancestors died of arteriosclerotic causes—cerebral hæmorrhage, interstitial nephritis, angina pectoris. Otherwise negative. P. H. Always healthy and active. Had the usual diseases of childhood. Lobar pneumonia at twelve years. Typhoid fever (?) at fifteen years. No venereal history. No migraines, dyspepsias, or other manifestations of the lithæmic diathesis. Acute follicular tonsillitis one year before the P. I., otherwise no acute infections other than an occasional coryza or laryngitis, during the eight years preceding it. Health unusually good at the time of onset, not leading a very sedentary life, though a student, and not doing any heavy muscular work nor liable to exposure.

P. I. In the latter part of May, 1901, the patient woke one morning with a sensation of stiffness at the inner side of the left ankle. This sensation disappeared during the day, to reappear the next morning with increased severity. On

the fourth day after this was first noticed, the front of the inner malleolus was found to be very tender on pressure. Examination showed that there was a firm and very tender cord running over that region, movable between the skin and the bone, and the veins of the lower extremity being rather large in caliber, it was possible by a comparison with the unaffected ankle to make sure that the cord was the obliterated internal saphenous vein in the lower part of its course. There was slight superficial redness and very slight œdema, confined to the malleolar region. Spontaneous pain was not marked, but walking was difficult, and there was some lameness for the next ten days or two weeks. At the end of this time the acute symptoms had subsided, tenderness had disappeared, and nothing remained but the tough cord, about 3 cm. in length, in the situation described. Careful and repeated examination of the foot and leg, and of the whole body, failed to reveal any, even the slightest, local infectious process; Hb. was 110%, and the general health, as always, excellent. The patient went on taking regular but not excessive exercise, and thought little of the incident.

Early in July of the same year the patient seemed to be wakened in the morning by a sharp, burning, almost intolerable pain in the left ankle and lower leg, and found that there was a thrombotic cord, continuous with the first one, extending some six inches above it along the inner side of the leg, and corresponding to the course of the saphena magna. There was already considerable œdema, confined to the inner half of the leg and ankle, not extending to the foot. There was some superficial reddening, not limited to the line of the vessel, and the surface temperature was higher than on the unaffected side. Tenderness was extreme. Prolonged immersion in a stream of cold water was effected several times a day, with the result of moderating the pain, and enabling the patient to walk about. The affection did not, at this time, progress further up the vein; the pain, heat, swelling, and tenderness gradually disappeared. At the end of two weeks the leg was again in normal condition subjectively, and showed on examination nothing but the characteristic firm cord at the site of the obliterated vessel. General health continued unimpaired, even when the pain was greatest; there was never any elevation of body temperature, and the leucocytes, counted twice during the acute stage, were below 8000 per cu. mm. One subjective feature of considerable interest at this time was that on waking in the morning pain was always intense, and it was often necessary for the patient to hop to the bathroom, when the cold water running over the leg for fifteen minutes would make it possible for him to put the left leg to the ground without agony. During the morning, in walking about, the pain would grow constantly less, returning to some extent always after sitting for any length of time; but by the middle of the afternoon it was usually possible for the patient to play a game of tennis without consciousness of pain or fatigue. This pain, after the leg had remained long at rest, growing less the more the limb was exercised, was a very characteristic feature during all the acute exacerbations, and suggested the existence of a certain degree of periphlebitis.

During the summer and autumn the patient suffered from three more acute attacks—one about August 15, affecting the vein as high up as the knee, the next in the early part of October, obliterating the saphena to a point 5 cm. above the knee, and the final one just before Christmas, continuing the process up to within a few cm. of Poupart's ligament in the thigh. In onset and course all the attacks were precisely similar to those already described. General health continued excellent, there was no exposure nor injury nor strain of the leg, and the patient suffered from no infections. The onset was always during the night, there was never any premonitory symptom, such as tenderness of the unobstructed portion of the vein or sense of muscular constraint, before the onset of thrombosis, and the attack was always definitely limited from the beginning. That is, after acute symptoms had once appeared and a cord had been made out continuous with the old one already present, this new cord never extended during the same attack beyond its upper limit at the time of its appearance. During none of the later attacks was the body temperature found to be over 98.8°, and on one or two occasions inflammatory leucocytosis was determined to be absent, and Hb. 100% or above. Disability was great during these later recrudescences, especially when the vein became involved at the knee, and for two days at this time the patient was obliged to keep to the house. Œdema was never very marked, appearing only in the inner half of the leg and in the segment corresponding to the inflamed vein, never extending beyond the median line in front or behind, nor affecting the leg at all below the point of blocking. This absence of mechanical œdema was accounted for by the fact of the patient having very large and numerous veins in the extremities, with abundant superficial anastomoses. But neither then nor since has there been any indication of a varicose condition.

Looking back on this case, especially in the light of the facts to be mentioned later, is enough to fill one with wonder that such contemptuous disregard of the embolic possibilities of the situation did not meet with its appropriate punishment. Absolutely no treatment was carried out, except the local application of cold, and this solely to relieve pain. The patient even walked about recklessly when the suffering was quite severe and the local inflammatory signs were at their height.

This case is reported in some detail, because it is quite typical of all, and may have an added value from circumstances which made its exact and continued observation possible. During the last acute attack the patient consulted Dr. McCrae at the Johns Hopkins Hospital, and he agreed perfectly in the obvious diagnosis. The case is also of interest as one of thrombosis of a large vein successfully treated without local rest, and perhaps illustrates the extreme of what a thrombus may undergo in the way of mechanical disturbance without dislodgement and the production of embolism.

At the present time, three years after the last acute attack,

the obliterated fibrous cord of the left internal saphenous vein can still be traced up to the middle of the thigh. The vein is quite impervious. Collateral circulation evidently is perfect, and there is and has been no œdema. Sometimes when fatigued after long walking or after exposure, there is a sense of discomfort complained of in the affected leg, a feeling of tension, or as of being conscious of the presence of the cord. Otherwise there have been no local sequelæ.[1]

The patient has been under constant observation. His general health has continued vigorous, and there have been absolutely no symptoms which the most fantastic could attribute to the existence of the lithæmic diathesis.

Case II. Patient aged about 40 years. F. H. unimportant—no gout or rheumatism. P. H. unimportant; lues doubtful. For three years has suffered from Raynaud's disease, and has fairly extensive necrosis of digits of all four extremities. Over the site of the left internal saphenous vein is a line of brown pigmentation in the skin, extending from the inner malleolus almost to Poupart's ligament. Beneath the skin in this situation can be felt a fibrous cord, and there is no patent internal saphenous. The vein on the right side is patent. On inquiry, the patient says that some three or four years before the onset of his vaso-motor symptoms he suffered from several attacks of acute pain in the left leg, accompanied by great tenderness and some swelling, and lasting from two to three weeks at a time. The last attack affected the inner side of the thigh and occurred within four months of the onset at the ankle. The patient was in good health at the time, had not suffered from typhoid fever, and was certain that there was no sore or wound on the leg. There have been no subsequent attacks, and there is no persistent œdema. No other veins were ever affected.

Case III. Gaz. d. hôp., Paris, 1845, 2. s. VII, p. 86. Jadioux reports a case in a young man aged twenty, with a clear family and personal history. No lues and no suspicion of gout. There was a history of exposure to cold and wet for a short time; but the exposure was not of an extreme nature, was not unusual to the patient, and had never before been associated with disturbances of this or any other sort. On this occasion, after the exposure, the young man was suddenly taken with great pain in the middle of the thigh, abruptly and without any prodromal sensations, and followed by the classical signs of phlegmasia alba dolens. The total duration of the illness was four months, there being two or three distinct phases of acute recrudescence of the venous inflammation, separated by periods of quiescence. The veins affected were apparently the external iliac and crural vessels of the left side. There was no fever or constitutional disturbance at any time, and the patient made a complete recovery.

Case IV. Gaz. d. hôp., Paris, 1864, XXXVII, p. 345. Frémy reports the case of a shoemaker, an old soldier, aged fifty-six. F. H. negative. P. H. Always strong and healthy. Tripper twice, some years before; no lues. Twenty years before was in hospital some weeks with "sciatica"—otherwise had never been sick. There was no suspicion of gout or rheumatism in this patient or his family.

In December, 1861, the patient was taken with sudden lancinating pain in the calf of the left leg. There had been no injury, excessive strain, or local or general infection. The pain became intermittent, was not at any time severe, and disappeared within a week or so. A month later acute pain in the same region was experienced, this time so severe as to incapacitate the patient for work, and swelling and tenderness of the calf were noticed. At the end of two weeks the œdema disappeared, and the pain became slight enough to enable the patient to return to work, though it persisted to some extent. In February, 1862, after a long walk, the patient was again attacked by sudden severe pain in the left leg, from the site of the previous trouble up the inner side of the knee, and along the middle of the thigh towards the groin. On the following day œdema appeared in the foot, soon implicating the whole limb up to the middle of the thigh. The patient was quite unable to work, and one week later was admitted to hospital. Examination revealed an extremely sensitive firm cord occupying the position of the saphenous vein and extending up almost to the level of the saphenous opening. The œdema of the leg was massive, the skin cool. There was no fever and no constitutional disturbance. Mercurial treatment was instituted, and with rest and local applications, the local condition improved. During the patient's stay in the hospital, and after intervals of complete quiescence, he suffered from two recrudescences of the inflammatory condition in the course of the vein previously affected. Two months after admission the patient left the hospital with the leg in a perfectly normal state. Frémy is disposed to suggest the peculiar sedentary attitude required by the patient's trade as the determining cause of the thrombosis.

Case V. Anfiteatro anat., Madrid, 1880, VIII, pp. 127, 140. E. Delgado-Villadiego reports the case of a man aged fifty-two, corpulent, of sedentary habit, and a gross feeder. He was not luetic, and had a clear family and personal history, with no suggestion of gout or rheumatism. He was

[1] At the present time (April, 1905), this patient has just recovered from a further recurrence of his affection, the first one in nearly four years, implicating one of the small veins on the dorsum of the foot. The onset was typical, constitutional disturbance nil, no local or other cause was present, acute symptoms lasted about ten days, and the occluded, slightly tender vein is distinctly palpable. Dr. T. C. Janeway had recently very kindly put in my way a reference to a case of Dr. Schwyzer's, in which recurrent thrombosis had been associated with a very rapid blood coagulation time, great diminution of chloride output, and calcium retention, proven later to depend on the presence of fluorine in beer drunk by the patient. I was able to investigate these matters in this last attack suffered by my own patient, and found his blood coagulation time in the acute stage to be from 2½ to 3¼ minutes, and his urinary chlorides constantly above 9.5 grammes in the 24 hours. In this connection the low blood coagulation time observed at one examination in Case VII of this series is of suggestive interest.

suddenly taken with pain and swelling in the calf of the left leg, and the first medical man called in wanted to incise what he thought must be a deep abscess. From this time through a period of five months the patient suffered from repeated attacks of clearly recognized thrombo-phlebitis of the femoral veins, both sides being progressively affected, with alternating periods of quiescence and flaring up of the acute symptoms in successively higher stretches of the vessels, until they were both occluded practically up to Poupart's ligament. There was at no time any fever or disturbance of general health. Mercurial treatment was employed, and recovery was satisfactory, with no œdema. The detailed history of the recrudescences is practically that recited in connection with Case I.

CASE VI. Gaz. méd., Paris, 1891, LXII, p. 327. Muselier reports the case of a man aged fifty-eight, not gouty, who had had lues and smallpox many years before. No injury, local or general infection, cachexia or anæmia in connection with his present illness. The patient was taken with sudden intense pain in the left upper arm, with rapidly developing œdema below the site of pain. Thrombosis of the deep brachial vein just below the axilla was made out on examination. Bandaging below the block was resorted to in order to control the massive œdema. At the end of a month recovery was complete, without any succeeding relapses, and no other veins were affected. As in all these cases, constitutional disturbances were marked by their absence. Muselier has no suggestion to make as to etiology. The only plausible cause not absolutely excluded by his report, however, is the very remote possibility of the unrecognized presence of a cervical rib, with consequent pressure. Axillary tumors were excluded. The absence of repeated relapses and new attacks, and the localization in the upper extremity, make this case and the next rather different from the rest.

The following notes concern a case which was admitted to Dr. Osler's service shortly after this paper was first presented to the Johns Hopkins Hospital Medical Society. In the localization of the disease process and in the absence to date of any recurrence the case resembles Muselier's, above. But the clear history, the apparent clinical spontaneity of the lesion and the fact that Dr. Osler and Dr. Thayer both examined the patient, make it seem justifiable to include this case with the preceding one even though the course of events in them does not admit the adjective "recurrent" in the title under which this is written.

CASE VII. A young American, age twenty-two, was admitted to the Johns Hopkins Hospital October 20, 1904 (Hospital No. 48,606), with the diagnosis of thrombosis of the axillary vein. F. H. Negative as regards gout, rheumatism, or other dyscrasias. P. H. Typhoid fever ten years ago; otherwise always healthy. The patient has always been active, is of a slightly neurotic temperament, and is in a business which requires no particularly sedentary or otherwise unusual physical life. No antecedent general or local infection.

P. I. No history of exertion except carrying a suit case while travelling. On October 20, 1904, at 1.30 p. m., the patient remembers shaking hands with a friend, when his arm and hand were quite normal. A little later, on again shaking hands, he felt a slight twinge of pain in the right elbow and a sensation of coldness in the hand. Half an hour later the hand was distinctly swollen and very numb. The patient immediately consulted a physician and while with him the circumference of the right arm increased one inch in half an hour. Massage was tried without benefit; as the œdema was rapidly increasing the patient came to Baltimore and saw Dr. Thayer. He was admitted to the hospital at 10 p. m. of the same evening.

At 8 p. m. Dr. Thayer made the following note: "Healthy-looking man; right arm, forearm, and hand greatly swollen and of deep-blue cyanotic color and quite cold. The peripheral veins from the hand up are prominent and exceedingly tense. In the outer axilla the vein stands out suddenly and sharply as a hard knuckle—clearly the beginning of the thrombus. The swelling extends up over the deltoid region and is perhaps more marked in the upper arm. The measurements, 20 cm. below tip of acromion are, on the right, 33.4 cm., on the left, 26.5 cm. The right radial is palpable."

The next day Dr. Osler made this note: "Arm not so livid as last night. Veins on back of hand not so prominent. Hand is warm. Diffuse redness up to middle of arm. Radial well felt. There is a line of demarkation of redness above insertion of deltoid. No soreness of clavicle."

The temperature ranged from 98° to 99.6° for the first six days and was normal continuously after October 26. The urine was negative. On October 21 the leucocytes were 11,600. On October 25, 12,700.

On October 25 I saw the patient in the ward, when his arm was in the condition above described. Pain, which had been considerable for the first few days, was becoming less, though the arm was very tender to touch and even slight passive motion caused distress. A most interesting feature that is not noted in the history was that the patient had, for so young a man, a very marked degree of sclerosis of the superficial veins of both upper and lower extremities—a fact that cannot but be of really considerable significance. On October 25 the coagulation time of the patient's blood was between one and a half and two minutes.

On November 17 the patient's improvement having been steady if gradual, and the arm apparently normal, the patient was discharged. No note was made at this time of the condition of the vein at the point of blocking. There had been at no time any constitutional symptoms other than those of a neurotic nature.[1]

There have been in the hospital recently two very interesting cases of femoral phlebitis whose records I have had the privilege of examining. One of these, a man who was in

[1] Dr. H. W. Cook, who has recently (April, 1905) seen this patient, informs me that the fibrous cord of the obliterated vein is easily felt and identified in the patient's axilla.

Ward F in September, 1904, died suddenly from embolism of the pulmonary artery. In neither of these house cases was the cause of the thrombotic process definitely determined; but as both patients had some pus in the urine, and as their phlebitis was attended by some fever and other general constitutional symptoms, it has been thought best not to attempt to include them in this series of cases.

These seven cases constitute the whole of the material that I have to report. There are hosts of articles scattered through the literature professing to deal with instances of spontaneous phlebitis, but on going through these papers it is found in nearly every instance that the authors are reporting cases of phlebitis in association with anæmia, typhoid fever, or other infections or cachexiæ, or cases in which these or some of the other recognized factors in the production of thrombotic processes cannot be excluded. I have included no cases in which the epithet "spontaneous" has not seemed beyond criticism just, in the present state of our knowedge. The only other instances of which any record has been available are those reported in the thesis of Daguillon.[3] He details accounts of five original cases, resembling in all essential particulars those reported here, except that the author feels constrained, or enabled, to label all the patients "non-gouty arthritics," and refers these and seven other cases collected from the literature, to the influence of the lithæmic diathesis. It is interesting that of the twelve cases reviewed by the French author, three died of embolism, and there were altogether six patients afflicted with embolic sequelæ of greater or less severity. Some of Daguillon's conclusions are of interest. He says:

"There is a primitive form of phlebitis, *i. e.*, one without any immediate determining cause."

"Primitive phlebitis is an indication of a general diathetic influence, shown in an arthritic constitution, with or without actual gout."

"It has a special clinical picture—that of limited, localized, superficial phlebitis, affecting the lower limbs, causing slight local and no general reaction. It is of slow evolution, and shows a progressively ascending march by successive attacks and relapses."

"The prognosis is serious, owing to the facility with which embolism occurs."

Daguillon believes that the process is mainly a parietal thrombosis, and that complete and final fibrous obliteration of the vein occurs as rarely as does suppuration, which is never. In the cases which I have been able to examine, there has been no doubt possible as to the permanent obliteration of the vein after the subsidence of the acute process, and this seems to have occurred just as certainly in the cases collected here from other sources.

It is as well to admit without reserve that the picture here presented is practically identical with that described by Paget[4] for gouty phlebitis, and that I can find no other variety of phlebitis from any cause running such a peculiar and characteristic course. But that does not seem sufficient cause for following Daguillon, and subscribing to Tuckwell's dictum, that all so-called spontaneous phlebitis is in reality the phlebitis of gout. It may be considered suggestive that one of the present series was a sufferer from Raynaud's disease, which Haig at least would definitely associate with the state of uricacidæmia. But that particular instance is one of the least satisfactory here reported, and could be dropped from consideration, and still leave a body of cases in which the ascription of the lithæmic, or of the even more generously inclusive "neuro-arthritic," diathesis, would require a facile imagination. It is true that Hirtz and Hannequin,[5] in a suggestive paper on venous heredity, hold that among arthritic families the diathesis may manifest itself solely by a tendency to varices and to phlebitides from slight causes, with great liability to relapse of the latter. They wish to connect the tendency with a general condition of weakness of the connective tissues in these families, and report cases of phlebitis from different causes occurring with unusual frequency in members of the same family.

A family and personal history of great interest in this connection has been referred to me by the kindness of Dr. Wilder Tileston of Boston. The patient, a man of thirty-five years, has since 1887 passed through eight attacks of thrombophlebitis in the lower extremities, almost without doubt of the same type as the series reported. The case is not included with the indubitably "idiopathic" group at this time, because it is vaguely possible that some at least of these eight thromboses may have been associated with an anæmia. Of sixteen adult individuals among this gentleman's ancestors and collateral relatives, eight have shown a marked susceptibility to venous disease, in the manifestation of varices and hæmorrhoids or in extreme liability to thrombosis in the puerperium or following the acute infections. In other respects, the family history seems beyond the grasping criticism of the uricacidists.

However valid Hirtz and Hannequin's assumption may be for the cases they report, and without accusing the more fervid of the supporters of the lithæmic diathesis of attempting to make it cover too great a variety of physiological sins, it certainly seems unlikely that the present cases can be brought under the arthritic ban. Excepting the case with symmetrical gangrene, not one of the patients showed any manifestation either of gout or of the large number of ills that have been referred to uric acid; in all the cases, the family histories were quite clear of anything referable to this taint. It does not appear to be justifiable to qualify a phlebitis as gouty, simply and purely because it is apparently spontaneous, nor altogether because of its similarity in course to other inflammatory conditions of supposedly gouty origin.

Admitting then, for the moment, that we are ignorant of the pathology and causation of the cases here considered, the

[3] Thèse de Paris, 1894.

[4] St. Bart. Hosp. Reports, 1866, II, p. 82.

[5] Bull. méd. Paris, 1901 XV, p. 389.

following etiological suggestions may not be out of place. We are familiar with the predilection of thrombotic processes within the arteries for such portions of the vessel wall as are affected by arterio-sclerosis. The acute and inflammatory affections of the endocardium are specially prone to attack valves already damaged, by preference over those with unaltered endothelial coverings. We also know that phlebosclerosis is a condition quite analogous anatomically to arterio-capillary fibrosis, that it is frequently associated with the latter condition, may occur very early in life, and has hitherto attracted rather a curious interest, as having no particular significance. May it not be that the cases of venous thrombosis with which we are dealing depend for their immediate and localizing cause on such sclerotic changes in the walls of the veins? If a cachexia may determine the production of a thrombus within an artery, it seems very easy to believe that with the much slower current of the blood within the veins, an extreme or even beginning phlebo-sclerotic change might determine the deposition of a fibrin coagulum from the blood stream. Sclerotic alterations of the vein walls are often observed to progress by fits and starts, at times with great rapidity, and then to remain in a stationary condition for many years. It is suggested that such a rapidly progressive stage of the fibrosis, if associated with a small, even at first a purely parietal thrombus, might produce just such a series of phenomena as are shown by the present group of cases. The often insignificant—and probably often unrecognized—symptoms of the first onset, the peculiar progression of the affection through the continuity of the same vessel, successively attacking higher and higher stretches of the damaged vein, the almost constant story of good general health during and between the attacks—all these considerations suggest that if a constitutional fault, a diathesis, is at the bottom of these apparently idiopathic occurrences, that diathesis or fault is far more likely to be one concerned with the wall than with the contents of the vessel. It is an anatomical, rather than a chemical, depravity, of the constitution that is the affliction of these patients. It is realized that all this is very theoretical pathology—it is put forth very tentatively, subject to critical correction, and with hope that actual laboratory studies of the true pathological condition will serve either to substantiate or to correct the views so roughly sketched. It is noteworthy that all of the cases which I have been able to examine showed beginning sclerotic changes in the superficial veins of the extremities, in association with some degree of thickening of the arteries, though in only one instance (Case VII) was the change at all extraordinary, being in the others less than is seen every day in a multitude of persons who so far as we know have never suffered from thrombosis. The absence of fever and the fact that suppuration of the thrombus has never been observed in these idiopathic cases would support the view that they are not caused by obscure infections.

In conclusion, it may be noted that the prognosis of idiopathic recurrent thrombo-phlebitis is, as given by Daguillon, rather unnecessarily grave. Twenty-five per cent mortality seems extraordinarily high, and may probably be ascribed in his series to the fact that from their very nature, and the usual relative mildness of their symptoms, the large majority of these cases that occur will fail to find their way into medical literature. Some at least of the patients may walk about with an actively progressing thrombosis. That this may, with those ignorant of their risk, increase the danger of embolism over that suffered by the recumbent typhoid patient with phlegmasia, is unquestionable. It is also beyond doubt that a thrombus will often stand a great deal of manipulation. Still, none of us would care to allow a subject of this affection to roam about with no restraint but that imposed by pain, considering the recorded score of fatalities as it stands at present. And yet the alternative, that a busy man should be kept idle or recumbent for a long period, that may extend over the greater part of six months, by an affection in itself almost insignificant, seems ridiculous. An attempt to carry out such a measure with the average American would undoubtedly end in failure, and might result in sending the patient into other and less careful hands. When an obliteration of the lower part of the saphenous vein occurs in an otherwise healthy man, and is followed after recovery and a period of quiescence, by a second apparently spontaneous phlebitis in a higher part of the vessel, it would appear to be advisable to cut down over the saphenous opening under cocaine, and to ligate the vein at its termination. Such a procedure would at once obviate any further danger of embolism, and would necessitate only a short and definite period of confinement. When the phlebitis starts out in the very characteristic fashion above described, the chances are strong against it stopping short of the upper part of the thigh; the vein is doomed in its whole ength, and in any case its dangerous contents could be more comfortably supported with a firmly tied knot of good silk between it and the lungs.

STUDIES IN TYPHOID FEVER.

SERIES I-II-III.

The papers on Typhoid Fever, edited by Professor William Osler, M. D., and printed in Volumes IV, V and VIII of the Johns Hopkins Hospital Reports, have been brought together and bound in cloth.

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The price is $5.00 per copy. Address The Johns Hopkins Press, Baltimore, Maryland.

A REPORT OF SOME OBSERVATIONS ON HEART-BLOCK IN MAMMALS.[1]

By Joseph Erlanger, M. D.,
Associate in Physiology, The Johns Hopkins University.

Through the courtesy of Dr. Osler the author has had the opportunity of making observations on a case of Stokes-Adams disease in which the disturbances in the circulatory system obviously owed their origin to the condition now generally termed heart-block. The studies made of this case indicate that when the block is complete the auricles respond normally to influences exerted upon the heart through its extrinsic nerves; but the ventricular rate seems to be influenced neither by changes in posture, nor by atropin, nor by moderate muscular exercise. However, the ventricular rate may be increased by more severe muscular exercise. On the other hand it could be shown that when the block is partial not alone the auricles but also the ventricles, the latter within certain limits, respond normally to extrinsic influences. The characteristic attacks of unconsciousness are always associated with a very marked slowing of the rate of the ventricle; the intervals between the beats may be twelve seconds. The slowing of the ventricular rate always precedes the cerebral symptoms by an appreciable interval.

These observations led to an attempt to produce and to study heart-block in mammals by methods that do not involve destruction of all the tissue in a cross-section of the heart.

After having made some preliminary and more or less successful attempts to produce heart-block in the dog, a simple and satisfactory method was devised of clamping the limited region in which lies the only muscular connection between the auricles and the ventricles, the auriculo-ventricular bundle of His. The method is not particularly difficult, and since it has been perfected the clamp has been successfully applied in every attempt.

When the clamp has been put in the right place the heart will continue to beat with undisturbed rhythm. But when the arms of the clamp are cautiously screwed together, the normal sequence of the auricular and ventricular beats will more or less abruptly give way to a partial block in which the beats of the auricles are to the beats of the ventricles as 2 : 1. With further clamping a 3 to 1 rhythm may be established and this, as a rule, passes into complete block in which the beats of the ventricle are totally independent of those of the auricle. The reverse order of changes is obtained when the clamp is unscrewed. As a rule the changes of rhythm occur at once, that is, without a preliminary stoppage of the ventricle.

In two experiments upon tightening the clamp the normal sequence gave way to complete block without passing through the usual intermediate stages. In these instances at the moment the complete block was established the ventricular rate was markedly slowed and the blood-pressure fell to a very low level. Thus in one of the instances the interval between two ventricular contractions was twenty-one seconds. The ventricular rate and the blood-pressure then gradually increased until values usual for heart-block were reached. The exact cause of this phenomenon has not yet been determined.

With each change in rhythm the blood-pressure is materially affected, falling when the ventricular rate is decreased and rising when the ventricular rate is increased. But even in complete block a fair pressure may be maintained.

When the block is partial both the auricle and ventricle may be inhibited by stimulation of the vagus nerve at least as easily as under normal conditions. But when the block is complete no diminution, or but very slight diminution of the rate of the ventricle results from stimulation of the vagus. The auricles react normally to vagus stimulation. Section of both vagi has little or no influence upon the rate of the ventricle when the block is complete.

Stimulation of the accelerator nerve as a rule increases the rate of the ventricle in complete block. The increase may be as great proportionally as that obtained under normal conditions. The reaction of the auricles to stimulation of the accelerator is not influenced by the block.

The rate of the ventricle in complete block is not as a rule materially affected by variations in the blood-pressure produced, for example, by compression of the abdominal or thoracic aorta or by extreme hæmorrhage.

The plugging of one coronary artery, either the right or the left, by Porter's method, has not obviously altered the rate of the ventricle in complete block.

In every case of failure to obtain block in the preliminary experiments it was found at autopsy that the ligature or clamp had not been placed so as to grasp the region of the auriculo-ventricular bundle.

The analogies between the phenomena of heart-block in the dog and the signs and symptoms of Stokes-Adams disease are obvious, and we may therefore be justified in predicting that the location of the lesion will be found to be the same in both conditions.

[1] Abstract of paper read before the Johns Hopkins Medical Society, March 20, 1905.

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THE FORCE OF CONTRACTION OF THE GALL-BLADDER AND THE COURSE OF ITS MOTOR AND INHIBITORY NERVE FIBERS.

By J. A. FREESE.

(From the Physiological Laboratory of the Johns Hopkins University.)

In response to an inquiry from Professor Halsted regarding the force of contraction of the gall-bladder it was found that no data could be obtained from the literature, bearing upon this point. The series of experiments described below was therefore undertaken in the physiological laboratory under the direction of Professor Howell for the purpose of determining the force of contraction of this organ. The work was afterwards extended to take in a study of the path of its nerve fibers, since evidence was soon obtained that the musculature of the bladder is supplied with inhibitory (or dilator) nerve fibers as well as with motor (or constrictor) fibers.

METHOD OF RECORDING THE MOVEMENTS OF THE GALL-BLADDER.

All of the experiments were made upon dogs. The animals were given one grain of morphia hypodermically an hour before the operation began. Throughout the experiment complete anæsthesia was maintained by administering ether through the trachea from an ether bottle. A metal canula was introduced into the gall-bladder and was then connected by means of lead tubing with a suitable water manometer. This manometer was provided with a float, bearing a pen for recording the changes in pressure. The canula and tubing throughout was filled with Ringer's solution.

The canula, about 20 cm. long, was made of brass tubing with an outside diameter of 3.25 mm. and a bore of 2.7 mm. in diameter. The end of the canula inserted into the bladder was slightly bent and was provided with three openings. To insert the canula the duodenum was cut open opposite the mesenteric attachment, and the papilla showing the opening of the bile duct was found. Through this opening the canula was introduced into the duct and pushed carefully along until its bent end lay well in the interior of the bladder. The canula was fastened by a ligature applied to the bile duct just outside the duodenum. Some difficulty was experienced at first in obtaining a perfectly accurate recording float, but the device shown in Fig. 1 was finally adopted, and has proved so satisfactory that it merits a special description. This float is made of a gelatine capsule, as follows: The top of a No. 3 capsule is removed and a hole about 0.7 mm. in diameter is bored through its center. The cap piece of a No. 4 capsule is then taken and prepared with a similar hole in its center. It is trimmed as much as possible, until only the cap-like end with its central hole is left. This latter piece is shoved into the bottom piece of the No. 3 capsule; the cap-piece of which with its central opening is then put in place. The stem of the float consists of a slender glass rod prepared from tubing by drawing it out in a flame. This stem is shoved through the hole in the top of the capsule and then down through the hole in the cap-piece previously inserted into the bottom of the capsule. The stem is thus held firmly at two points. The upper end of this stem, after passing through the cap of the manometer is bent at right angles and drawn out to a writing point, which is kept against the smoked surface of the drum by a pendent weight. As the gelatine is soluble in water it is necessary to keep a layer of olive oil on the surface of the salt solution in the manometer. In practice a layer of oil of about 60 mms. or more, was used. This required about 2.5 to 3 cc. of oil. The lighter specific gravity of the oil was compensated nearly exactly by the weight of the float and stem so that the results obtained can be expressed in terms of millimeters of salt solution. In all the experiments made upon stimulation of the spinal nerves it was necessary to curarize the animal in order to avoid the mechanical effects of contractions of the trunk and abdominal muscles. A one per cent solution of curare was used, made up in normal saline. This solution was injected into the jugular vein until stimulation of motor nerves failed to give a muscular response. Artificial respiration was then maintained with warm moist air.

THE FORCE OF THE MUSCULAR CONTRACTION OF THE BLADDER.

As stated above no record could be found in the literature of experiments made to determine directly the force of contraction of the muscles of the gall-bladder.

Heidenhain, Friedlander, and Barisch have measured the secretion pressure of bile.[1]

Heidenhain determined the pressure in connection with that of the superior mesenteric vein as proof that bile is not formed by simple filtration from the blood. His results show that the secretion pressure may vary from 110 to 220 mms. of a solution of sodium carbonate. The experiments of Friedlander and Barisch were made upon guinea pigs. A canula was inserted directly into the bladder and the bile duct was tied off at the intestine. The maximum pressure found varied from 184 to 212 mms. water.

In my own experiments secretion pressure was of course excluded. To obtain if possible a maximal contraction of the gall-bladder the splanchnic nerve was stimulated by strong

[1] Heidenhain in Hermann's Handbuch der Physiologie, Vol. 5, part 1, p. 269 and Friedlander and Barisch, Reichert and Du Bois Reymond, Archiv für Anatomie und Physiologie, etc., 1860, p. 646.

induction shocks, or the electrodes in some cases were applied directly to the neck of the bladder, or finally the spinal nerves were stimulated. The bladder in all cases was put under a certain pressure to start with, and in estimating the work done by the contraction this pressure must be added to the actual increase caused by the contraction. Some of the experiments were made with curare and some without. When curare is not used care must be taken not to allow an escape of current to the muscles of the diaphragm or to sensory surfaces that might reflexly cause a contraction of the diaphragm. For a typical gall-bladder contraction see Fig. 2.

While numerous experiments were made, results that bear upon the present question were obtained only in six cases, as follows:

Animal	Point of applying stimulus	Bladder under a pressure of	Rise	Total Pressure
	Without Curare			
Dog 16	Electrodes on bladder	305. mm.	7. mm.	312. mm.
Dog 17	" "	305. mm.	8. mm.	313. mm.
	With Curare			
Dog 18	Peripheral end of splanchnic	190. mm.	26. mm.	216. mm.
Dog 25	Combined result from stim. 8 and 9 dorsal	197. mm.	21. mm.	218. mm.
Dog 26	Stim. L. splanchnic	200. mm.	14.5 mm.	214.5 mm.
Dog 28	" "	217. mm.	4. mm.	221. mm.

Since the results in the last four experiments were obtained under conditions in which the possibility of error from direct or reflex stimulation of the skeletal muscles was entirely excluded they give perhaps the most reliable data concerning the force of contraction of the bladder.

It appears from these results that the bladder is capable of contracting against a resistance such as is offered by a column of Ringers solution 214.5 to 313 mm. high. Moreover the sudden maximum increase of pressure from direct stimulation of the peripheral end of the splanchnic apparently falls below 30 mm. when the pressure against which the bladder is working is about 200 mm. It seems evident from these figures that the musculature of the bladder is comparatively weak and that its contractions are not at all comparable in force to those of the urinary bladder, which, according to Mosso,[2] may contract in the dog with a force sufficient to support a column of water two meters high. Indeed the maximum force of contraction of the bladder does not much exceed the maximum secretion pressure as determined by Heidenhain.[3]

The Motor and Inhibitory Nerve Fibers to the Gall-Bladder.

It has been shown by Heidenhain,[3] and especially by Doyon[4] that the gall-bladder and the bile ducts receive motor fibers by way of the splanchnic nerves. On stimulating the peripheral end of the splanchnic they got a contraction of the bladder. Doyon found also that stimulation of the central end of the splanchnic causes a reflex dilatation or inhibition of the bladder, but he was not able to obtain this inhibition by direct stimulation, that is, he got no evidence of the existence of peripheral inhibitory fibers. In some of my earlier experiments the stimulating electrodes were applied directly to the neck of the bladder where it passes into the cystic duct. It was found in some cases that when the electrodes were applied to the ventral side contraction of the bladder resulted, whereas, when placed upon the dorsal or dorso-lateral side a dilatation ensued (see Fig. 4). This result indicated the existence of inhibitory as well as motor fibers and an effort was made to trace out the origin of these two sets of fibers from the spinal cord with the hope that they might emerge by different roots. In later experiments the existence of inhibitory fibers in the splanchnic nerve was demonstrated successfully (see Fig. 5). Usually when the splanchnic nerve is cut and the peripheral end is stimulated by strong tetanizing currents a constriction of the bladder results; in some cases, however, the constriction is followed by a marked dilatation, and in other cases a marked dilatation only is obtained.

This latter result was obtained with dogs under morphia and a strong dose of curare. It seemed evident from these results that the splanchnic nerve is capable of causing either a constriction or a dilatation of the gall-bladder, and therefore probably contains both motor and inhibitory fibers for this organ. To ascertain the point of emergence of these autonomic fibers from the spinal cord numerous experiments were made. The procedure was as follows: The spinal cord was exposed with great care, and the hæmorrhage that occurred from the bones was controlled as the operation proceeded, so that the total loss of blood was quite small. The exposure was made for the region of the lumbar and lower thoracic nerves in some cases and in others for the lower and middle thoracic nerves. The spinal nerves on one or both sides were prepared and a ligature placed around each. No attempt was made to separate the anterior and posterior roots since in some of the animals at least it was not found possible. After the nerves were prepared the abdomen was opened and the canula was inserted into the bile duct and connected with the manometer as described above. Curare was then administered through the jugular vein until stimulation of motor nerves gave no response. Artificial respiration was maintained with warm moist air. After the curare effect was fully manifest the spinal nerves were stimulated as follows: Each nerve was ligated close to the cord and then cut between the ligature and the cord. The effect of this mechanical stimulation was noted and an interval of several minutes was allowed between each ligation. Afterwards the spinal nerves were stimulated in order, with an interval of four or five minutes between each stimulation. The electrodes used were carefully shielded with paraffine to prevent escape of current to the cord and induction currents of various strengths and rate were used for stimulation. It was not found, however, that rate of stimulation made any difference in the result, except that below a certain rate a stimulus otherwise effective

[2] Mosso and Pellacani, Archivs italiennes de biologie, I, 307, 1882.
[3] Studien des physiologischen Institut zu Breslau, 1860.
[4] Archives de physiologie, normale et pathologique, 1894, p. 19.

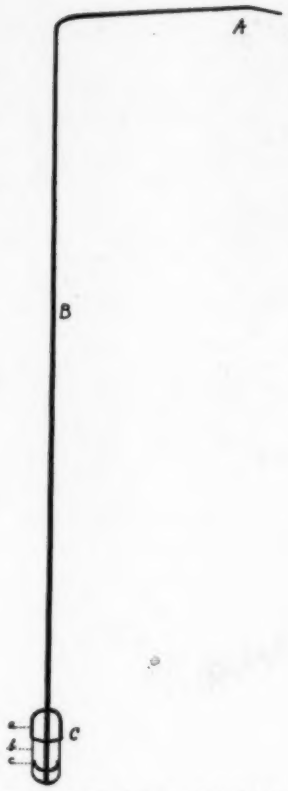

FIG. 1.—To show the float devised for this work, *A* is the writing point, *B* is the perpendicular stem, and *C* is the gelatine capsule. The top of the No. 3 capsule is designated by *a*, and its bottom by *b*. The inserted top of the No. 4 capsule is seen at *c*.

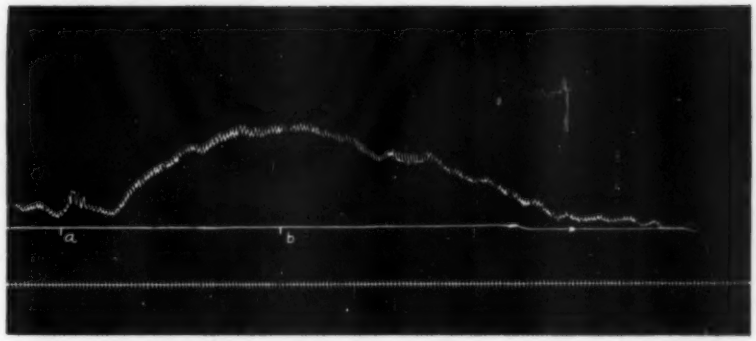

FIG. 2.—To show a typical gall bladder curve, resulting from stimulation of the peripheral end of the left splanchnic. Medium current on at *a* and off at *b*. Dog under curare. Time record indicates intervals of three seconds.

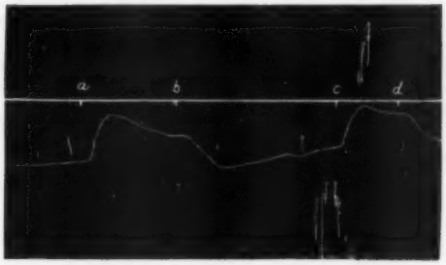

FIG. 3.—To show contraction upon applying the electrodes directly to the neck of the gall bladder. Stimulus on at *a*, off at *b*. Repeated for check (see *c* and *d*). This contraction was obtained in a curarized dog ten minutes after the animal had been bled to death by cutting the carotid.

FIG. 4.—To show dilatation upon applying the electrodes direct to the neck of the gall bladder. Dog under morphia and ether.

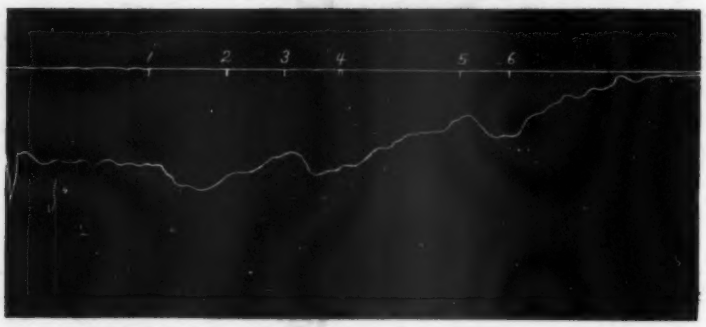

FIG. 5.—To show dilatation upon stimulating the peripheral end of the splanchnic. First stimulation (1 to 2), second stimulation (3 to 4), third stimulation (5 to 6). It will be noticed that there is also a gradual increase in bladder tone resulting from the repeated stimulation. Dog under curare.

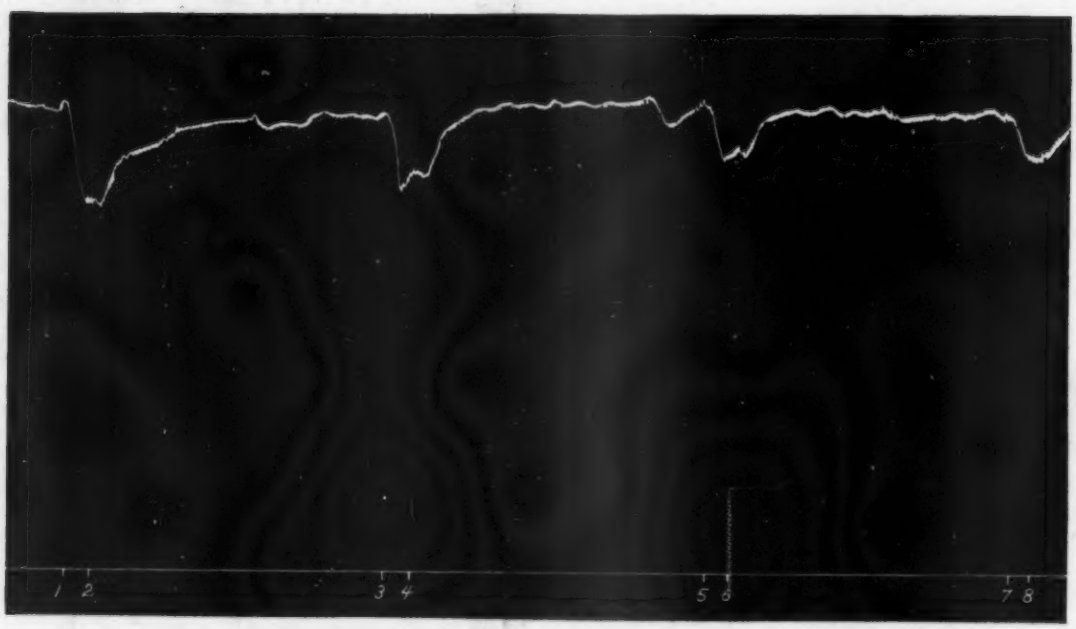

FIG. 6.—To show the dilatation upon stimulation of the spinal nerve roots. Stimulation of the eighth spinal nerve root (1 to 2). Stimulation of the ninth spinal nerve root (3 to 4). Stimulation of the tenth spinal nerve root (5 to 6). Stimulation of the eleventh spinal nerve root (7 to 8). Dog under curare.

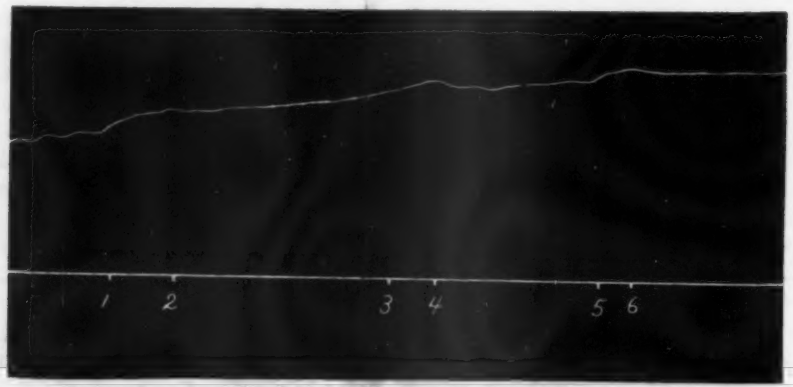

FIG. 7.—To show the contraction on stimulation of the spinal nerve roots. Stimulation of the twelfth spinal nerve root (1 to 2). Stimulation of the eleventh spinal nerve root (3 to 4). Stimulation of the tenth spinal nerve root (5 to 6). Throughout there is a constant increase in tone of the gall bladder due to repeated stimulation. Dog under curare.

became ineffective. As a result of this work it was found that the motor and inhibitory fibers leave the spinal cord in practically the same region, namely, from the sixth or eighth thoracic to the thirteenth thoracic spinal nerve. In some animals chiefly inhibitory effects were obtained, especially as the result of the mechanical stimulation on tying the roots. In others only the constrictor effects were shown. The results as regards the lower limit of emergence of these fibers were clear and constant. In no experiment were any effects upon the gall-bladder obtained below the thirteenth thoracic or first lumbar nerve. The upper limit was not defined so satisfactorily. In one case dilatation was obtained as high as the sixth dorsal and constriction as high as the seventh dorsal. The main outflow of the constrictor fibers occurs in the tenth, eleventh, and twelfth dorsal spinal nerves (see Fig. 7). The dilator fibers are most in evidence from the eighth to the twelfth dorsal nerves (see Fig. 6).

In these experiments the possible effect of contraction of the skeletal muscles upon the gall-bladder was eliminated, it is believed entirely, by the use of curare. It might be objected, however, that the variations in pressure in the bladder which were taken as proofs of constriction or dilatation as the case may be, might have arisen as the result of vaso-motor action upon the bladder or upon the liver. In connection with this possible objection it is interesting to state that upon several occasions both constriction and dilatation of the bladder were obtained upon stimulation of the splanchnic nerves after the animal had been bled to death (see Fig. 3). This fact would seem to show that the variations of pressure in the gall-bladder observed during these experiments were actually due to the contraction or relaxation of the musculature of the bladder itself.

CONCLUSIONS.

1. When stimulated through its motor nerves the bladder is capable of contracting against a pressure of at least 220 mms. of Ringer's solution, specific gravity 1.004. The maximum force of contraction exerted by the gall-bladder does not exceed materially the maximum secretion pressure of the bile.

2. The musculature of the gall-bladder is provided with motor (constrictor) and inhibitory (dilator) nerve fibers. These fibers are found in the splanchnic nerves.

3. Both the motor and the inhibitory fibers arise from the spinal cord in the roots of the sixth to the thirteenth dorsal nerves. The maximum outflow for the constrictor fibers is in the tenth, eleventh, and twelfth dorsal nerves. The dilator fibers appear slightly higher up and are most in evidence from the eighth to the twelfth dorsal nerve inclusive.

PROCEEDINGS OF SOCIETIES.

THE JOHNS HOPKINS HOSPITAL MEDICAL SOCIETY.

April 3, 1905.

Sarcomatous Myoma.[1] DR. CULLEN.

Dr. Cullen showed a specimen of this condition, removed from a woman of forty-two. Two years ago she had presented the usual features of a myomatous uterus which, with the subperitoneal nodule above it, was removed by the usual operation. The tumor was thought to be myomatous. In February, 1905, she was seized with sudden pain in the lower abdomen and was operated upon again. The abdomen was found filled with blood, and sarcomatous nodules were discovered springing from the cervix. Complete removal was impossible. Examination of the tumor removed at the first operation and thought to be a simple myoma showed sarcomatous degeneration.

Fibroma of Abdominal Wall.[1] DR. CULLEN.

This had been removed from a woman thirty years of age. Three years previous she had noticed a mass under the ribs which had grown slowly at first and later more rapidly. There had been some loss in weight. At operation a fibroma was found springing from the muscle sheath.

Primary Carcinoma of the Tubes.[1] DR. CULLEN.

The growth in this case had started from the Fallopian tubes, had involved the ovaries and studded the omentum. Pain on defecation had been a prominent symptom. A complete hysterectomy was done and six inches of bowel removed, the sphincter ani being preserved. The patient is still alive and feels well.

Accessory Omentum. DR. CULLEN.

A railway conductor, following a struggle with a drunken passenger, was seized with abdominal pain, showed a temperature of 101.5° and a leucocytosis of 17,000. There was no abdominal rigidity but an exploration was advised, and at operation a greyish mottled mass was found which proved to be a twisted accessory omentum arising from the union of the ascending and transverse colons.

Dr. Kelly, in commenting on Dr. Cullen's first case, said that the interesting question was now raised as to which myomata could be regarded as simple and treated as non-malignant, and in which ones the prognosis was bad. At any rate in these cases the uterus should always be laid open and examined carefully before the abdomen is closed. It is important also to determine how far these growths extend, for if they involve the mucosa the wisdom of supra-vaginal amputation—otherwise the operation of choice—would be doubtful.

The Electrical Theory of Matter. PROF. H. C. JONES.

Prof. Jones of the Johns Hopkins University gave a somewhat popular exposition of the recent work on radio-activity.

[1] These cases will be reported in full later.

The great problem of physics had always been, he said, to know whether there were several different elements or whether at bottom all were really one. Hydrogen, in early history and later other elements, had been thought to be the fundamental substance. The study of radio-activity really started with the work of Thomson who, working over the question as to whether or not the atom might be the ultimate unit, elaborated the corpuscular theory which defined the corpuscles as little pieces of matter carrying unit electrical charges and as really the ultimate units of matter. The mathematicians then showed that to account for the properties of the corpuscle no matter was necessarily assumable. Unit electrical charges moving at a high velocity through an elastic medium gave all the properties of mass and inertia which we ascribe to matter. This theory is now generally accepted. Following the work of Thomson came the discovery of X-rays by Röntgen. Then Becquerel found a remarkable radiation produced by uranium, and Schmidt, by thorium. This led to a careful study of pitch-blende by the Curies and the discovery of radium.

The Properties of Radium.—The element owes its interest to the fact that it does things no other form of matter does and to a degree never dreamed of. Its first remarkable property is its unique ability to transform itself into another element—helium. Its second phenomenal attribute is its ability —also absolutely unique—of giving out tremendous amounts of heat. These properties of the salt inhere not in the radium itself but in an "emanation" which may be distilled over from the radium bromide and which is constantly being "re-created" in exhaustless amounts. The "emanation" is also the source of the remarkable α, β, and γ rays; and it seems probable that a large part of the sun's heat may be due to the presence in it of radium in quantity.

Experiments on Amphibian Embryos. Dr. Lewis.

These experiments, reported by Dr. Lewis, were undertaken by him to throw, if possible, some light on the problems of preformation and epigenesis. The development of the lens and cornea were studied. The animals were operated on at the time of closure of the medullary groove and the object of the first series of experiments was to see whether a lens would arise from the ectoderm without the presence of the eye. A subcutaneous excision of the eye was done and the skin returned to its place. Serial sections of the animal were then examined at a later stage and no lens was found unless the eye had regenerated. In another series of animals the eye was transplanted, and in many of these cases a lens developed from the ectoderm over the misplaced eye. Even when an eye from one species was transplanted under the skin of another a lens, remarkably enough, was often found to develop. All the findings of the experiments spoke for epigenesis as against preformation.

April 17, 1905.

Comparative Surgery. Dr. Cushing.

The meeting was devoted to comparative surgery, a report being made of the work done in the course in operative surgery on animals by the third-year class of the Johns Hopkins Medical School. Dr. Cushing, by way of introduction, emphasized the importance of building up a veterinary hospital in connection with surgical teaching—not only for the teaching purposes proper but also by way of disarming the criticism, perhaps a just one, which was made against the reckless use of material involved in allowing students to operate on healthy animals. Operative surgery was usually taught by work on the cadaver; it was therefore confined to operations on the extremity and ligation of arteries. But the absolutely essential instinct for surgical cleanliness, the ability to handle living tissues, skill in controlling hæmorrhage—these things could not be learned from a cadaver. Nor was it possible to teach or to learn visceral surgery in this way.

When the course in animal surgery at the medical school was started, operations were done for hypothetical lesions. The material was not then necessarily wasted but could often be used in one of the laboratories; a gastrostomized dog, for instance, furnished the physiologists with gastric juice for study, and so forth. Nevertheless, this method involved needless operation; and criticism of this feature only began to be disarmed when animals were brought in with lesions which needed treatment. In the future, then, the plan is to build up a veterinary hospital so that animals may receive necessary surgical attention and students may receive useful surgical instruction at the same time.

Hæmorrhagic Cysts of the Thyroid.—Mr. Faris reported two cases of this condition occurring in dogs. The first was in an Irish setter. It had caused interference with respiration and cure was effected by its removal. The second occurred in a hound, was associated with bad temper, muscular twitching, loss of hair, increase in weight, and dryness of skin. No exophthalmus was present. The cyst was removed but without much improvement in the dog's condition. Both tumors proved to be thick-walled cysts containing dark-red grumous material made up of shadows of red-blood cells and cholesterin. The pathology of the thyroid in dogs was said to be similar to that in man. Hæmorrhagic cysts, while rare, were occasionally reported. Their etiology was still undetermined. Trauma probably plays a part, and changes in the vessel walls with rupture probably do the rest.

Utero-Vaginal Prolapse.—Mr. Thacher reported two cases. The first was an acute one complicating labor in a bitch. The vagina and cervix were prolapsed, the bladder was out of the pelvis, there was inability to urinate, and the animal was in bad condition. A uterus containing nine pups was removed and the prolapse reduced. Death occurred in fifteen hours, hydronephrosis and localized peritonitis being present. In the second case an irreducible mass protruded from the vulva and two operations were required to cure the condition.

Obstetrical complications were said to be common in animals and death often occurred without delivery. Acute prolapse was most frequent in the herbiverous animals and the immediate cause was often a very full uterus.

Inguinal Hernia in the Dog.—These cases were reported by

Mr. Beall. The first patient showed an irreducible right inguinal hernia with cystocele and the radical hernia operation was done. Death occurred on the second day; the dog showing ulcers of the stomach and an atrophied right kidney. The second patient had a bilateral inguinal hernia. The two sides were operated on at intervals and complete cure resulted. In the third dog the hernia contained the omentum and the round ligament. Hernia in the dog is a very common condition, the commonest variety being the mid-ventral. The inguinal form occurs much more often in the female than in the male, due probably to the occurrence of pregnancy and to the fact that normally a bitch has practically a patent canal of Nuck. In the male, too, the tunica vaginalis retains its connection with the peritoneum so that the anatomical facts alone do not explain the occurrence of inguinal hernia, which is relatively rare in male dogs.

Canine Tumors.—This series was reported by Mr. Ortschild. The first was an adeno-carcinoma of the breast with glandular metastasis. The complete operation was done. Death occurred from cancrum oris. Mixed teratomata over the breast and thorax were found in the second case. These on section showed cartilage, adeno-carcinoma, carcinoma simplex, and bone. In another dog a cyst adenoma of the breast was found and removed. This patient died from a phagadænic ulcer of the mouth. In a fourth case a mixed tumor of the breast, which had succeeded to a "milk-breast" following a bite, was found and removed. Cure resulted. An intracystic papilloma of the breast with metastases, a fibro-lipoma of the vaginal wall, and a hygroma of the right shoulder were also reported. The last tumor of the series was a pedunculated growth arising from the lower abdomen and just swinging clear of the ground when the dog walked. It was removed and proved on section to be an adenoma. Tumors—particularly carcinomata of the skin and mammæ—are common in dogs. Fibromata, enchondromata, and sarcomata of the breast are also seen.

Dr. Bloodgood showed the specimen of a melano-sarcoma of the liver occurring in a horse.

NOTES ON NEW BOOKS.

The Follies of Science at the Court of Rudolph II, 1576-1612. By HENRY CARRINGTON BOLTON. (*Milwaukee: Pharmaceutical Review Publishing Company, 1904.*)

This volume is intended to describe with historical accuracy the men, scientific, semi-scientific and otherwise who frequented the court of Rudolph II, Emperor of Germany, and to portray the scenes to be witnessed there in the sixteenth century. The first chapters of the book are devoted to Dr. Dee, an Englishman of great erudition, who undoubtedly was the dupe of his associate and helper, Kelley, a forger and pretender. He seems to have been a religious enthusiast whose sincerity alone relieves his name from the imputation of great guile. The tale of the residence of Dee and Kelley in Prague and Cracow and the return of the former to England to end his days in honor as the Warden of Manchester College, and the downfall of the latter to end his days in prison and by torture are well told. The chapter on seeking the Philosopher's stone is exceedingly interesting. The *wit* of the unknown Westphalian alchemist to whom Rudolph II had sent a messenger to invite him to his court is worthy of reproduction. The emperor received the epigrammatic reply: "If I possess the Philosopher's stone I have no need of the emperor; if I do not possess it the emperor has no need of me." The descriptions given of the "magistery" of the Philosopher's stone are varied and interesting. We are informed that some alchemists believed that it would transmute one hundred times its weight of mercury into gold; Roger Bacon on the other hand claimed for it a multiplying power of one hundred thousand and Hollander of one million. Most alchemists believed that mercury was essential for transmutation into gold, but "Töpfer made the important discovery that gold could be made out of Jews. He had found by experiment that twenty-four Jews yield by proper treatment one-half ounce of gold, so that by repeating the process daily with 100 Jews, making due allowance for holy days, 624 ounces of gold could be made in twelve months." The story of Tycho Brahe and also of Kepler and others who found a hospitable refuge at the court of Rudolph, is interestingly told. The concluding chapters on "Medicine," "Magic and Sorcery," and the "Decline of the Follies of Science," are very suggestive. The author shows how astrology gave us astronomy, alchemy chemistry, and the search for the Philosopher's stone many inventions and mechanic arts. He traces the rise of mathematics, anatomy, botany, and kindred sciences to the stimulation of thought which followed the vain quest after the six follies of science, the Quadrature of the Circle, the Multiplication of the Cube, Perpetual Motion, Judicial Astrology, Alchemy, and Magic.

The style of the book is pleasing and the contents are suggestive and profitable to all who are interested in medicine and the allied sciences.

A Text-Book of Legal Medicine. By FRANK WINTHROP DRAPER, A. M., M. D., Professor of Legal Medicine in Harvard University; Medical Examiner for the County of Suffolk, Mass.; Medico-Legal Pathologist at the Boston City Hospital, etc. Fully illustrated. (*Philadelphia, New York, London: W. B. Saunders & Company, 1905.*)

The well-known unpreparedness of the general practitioner to appear in court and his common disinclination to do so have been the main reasons why the author has prepared this admirable text-book. According to him the medical witness should possess the following qualifications: 1. The faculty of accurately observing all things about him and of making full notes of what he sees. 2. A retentive memory. 3. Sincerity, candor and a mind unprejudiced. 4. A well-balanced temper that will remain unmoved under provocation. 5. A gift of expressing tersely and intelligibly what is in his mind. To this it seems proper to add the advice of Blizzard, "Be the plainest of men in the world in a court of justice; never harbor the thought that if you do not appear positive you must appear little or mean; give your evidence in as concise, plain, and clear a manner as possible. Be intelligent, candid and just, but never aim at appearing unnecessarily scientific. If you can, make your evidence a self-evident truth. Thus though the Court may at the time have too poor or too mean an opinion of your judgment, they must deem you an honest man."

With the exception of Toxicology and the Medical Jurisprudence of Insanity (which in the opinion of the author require a separate consideration), the book is a comprehensive text-book of legal medicine. It is carefully and painstakingly written and contains what the unfortunate medical witness should know. The chapter on Death by Electricity seems especially timely. We know of no similar work of its size which contains so much.

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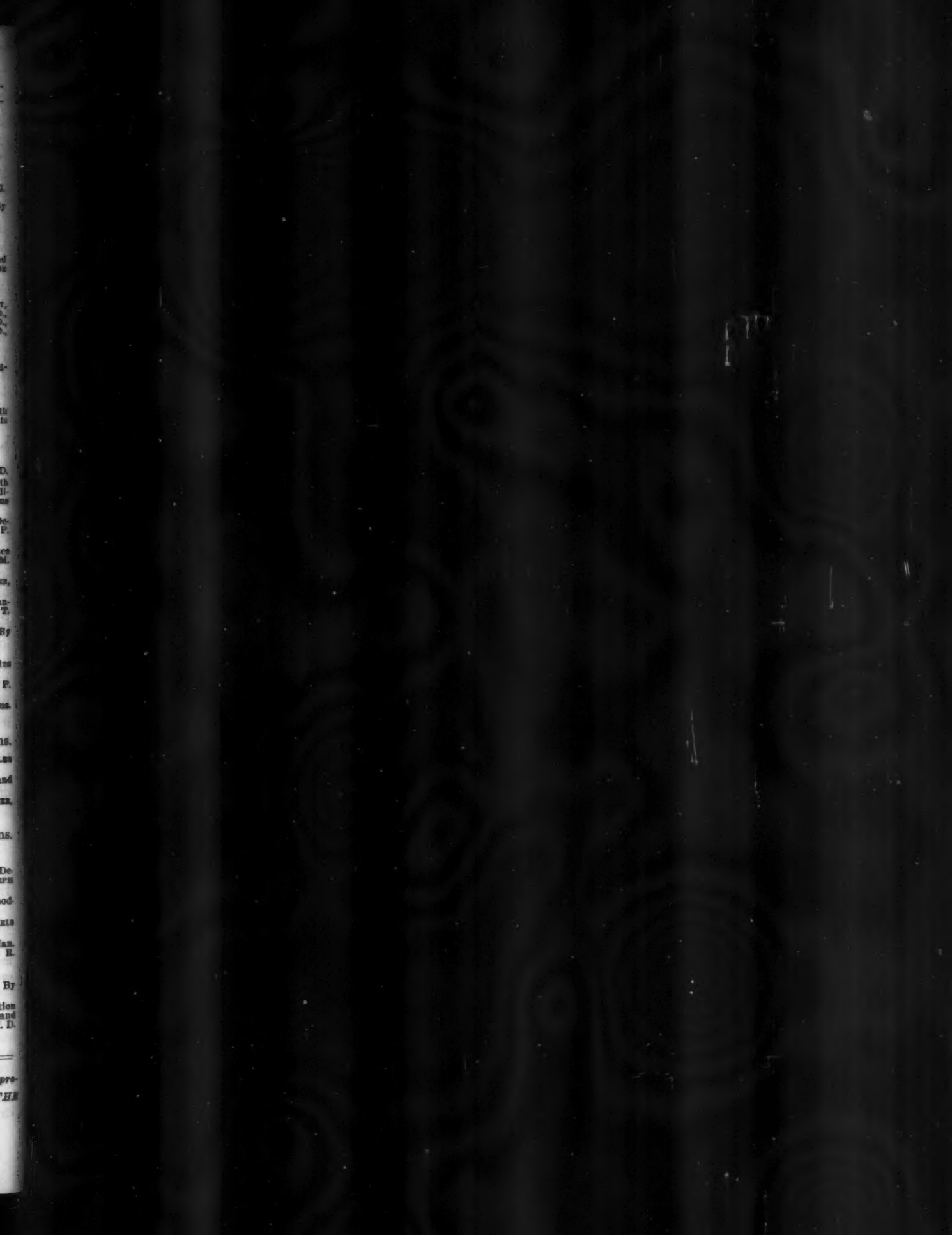
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